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DISPLAY SHELVES

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Vaseretic® is contraindicated in patients who are hypersensitive to any component of this product or to other sulfonamide–derived drugs and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.
Dosage must be individualized; the fixed combination is not for initial therapy.
Evaluation of the hypertensive patient should always include assessment of renal function.
For a Brief Summary of Prescribing Information, see adjacent pages.

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Vaseretic® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

TABLETS
VASERETIC®
(ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE)

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: *General; Enalapril Maleate; Hypotension:* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1.3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, *Drug Interactions,* and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. This may occur at any time during treatment. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions, Enalapril Maleate and Hydrochlorothiazide).*

Pregnancy; Enalapril-Hydrochlorothiazide: There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 ½ times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 ½ times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses; 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. (See *Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality,* below.)

Enalapril Maleate; Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats, and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide; Teratogenic Effects: Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4 - 5. 6 mg/kg/day (approximately 1 - 2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Nonteratogenic Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: *General; Enalapril Maleate; Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69*) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See *Drug Interactions.)*

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions, Agents Increasing Serum Potassium).*

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients; Angioedema: Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin converting enzyme inhibitors, including enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions; Enalapril Maleate; Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Hydrochlorothiazide; When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—additive effect or potentiation.

Cholestyramine and colestipol resins—Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

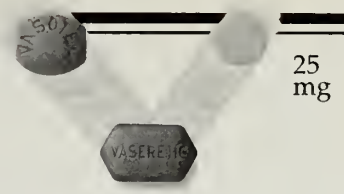
Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution



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assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse bone marrow assay.
Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.
Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.
Pregnancy, Pregnancy Categories C (first trimester) *and D* (second and third trimesters). See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*
Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain; *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia; *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth; *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo; *Skin:* Pruritus, rash; *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, *Cough.*
Clinical Laboratory Test Findings; Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.
Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*); *Cardiovascular:* Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; hypotension; angina pectoris; *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth; *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril has not been established. *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia); *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecomastia; *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing, photosensitivity; *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

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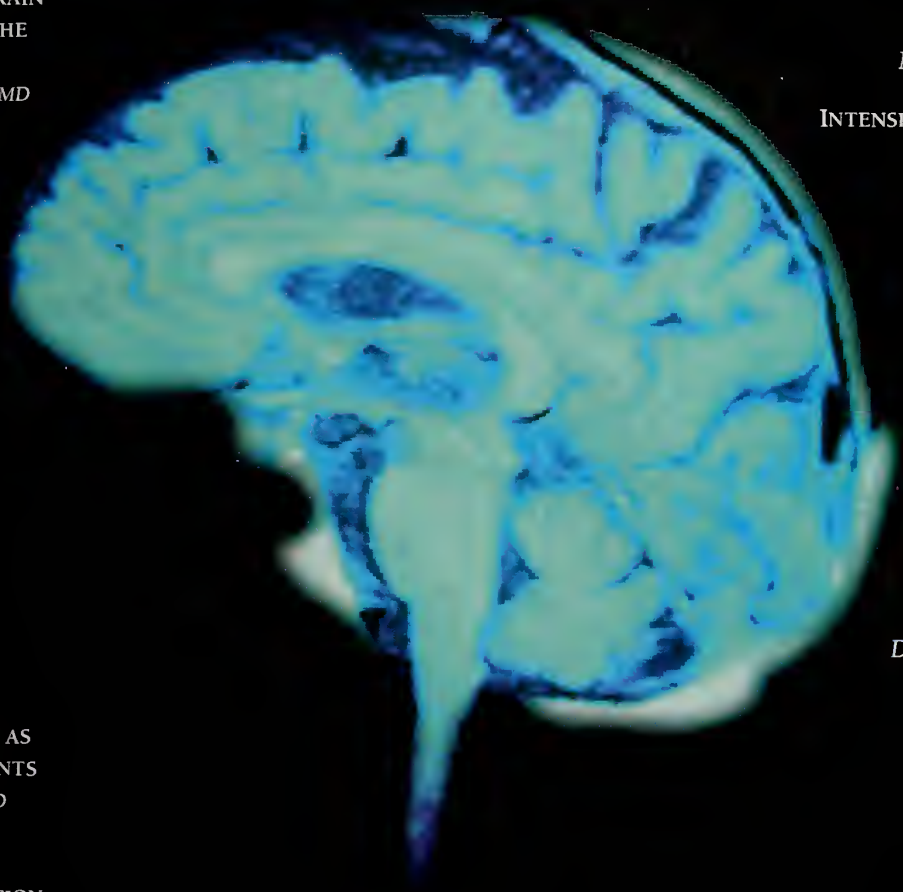

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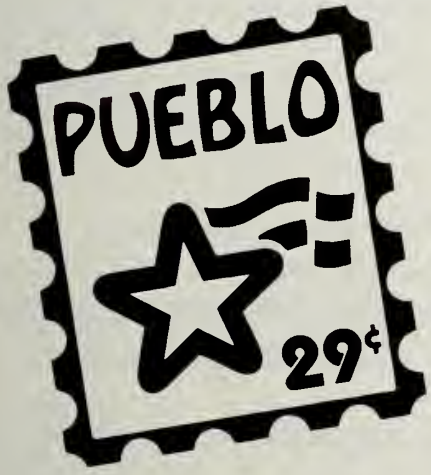

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2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
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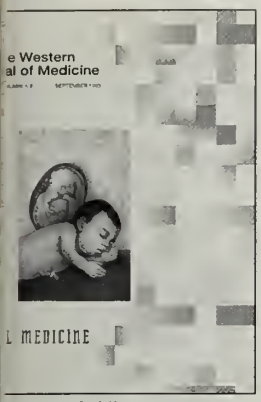

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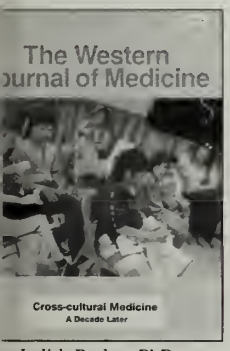

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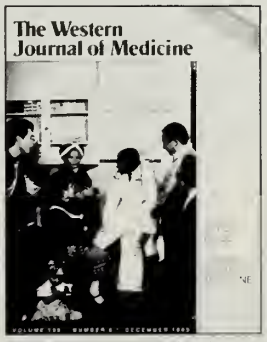

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Provides comfortable, prompt relief of allergic rhinitis and effective QD dosing

- Nasacort remains in the nasal mucosa with no measurable effect on HPA function [1-3]*

  Duration of acquisition of the PET image was approximately 55 minutes due to ^{11}C decay ($t_{1/2}$ of 20 minutes).[1] (n=2)

- Nasacort provides prompt relief for many patients — symptom reduction may occur as soon as 24 hours after starting therapy [4]
- Nasacort provides effective QD dosing — 2 puffs/nostril/day effectively controls symptoms in most patients; however, QD dosing can be increased to 4 puffs/nostril/day when necessary

Please see brief summary of prescribing information on adjacent page.

* In doses up to 440 mcg/day. [1]

Nasacort...Once Is Enough

QD STAYING POWER

ONCE DAILY
Nasacort® Nasal Inhaler
(triamcinolone acetonide)

Nasacort...Once Is Enough

ONCE DAILY
Nasacort® Nasal Inhaler
(triamcinolone acetonide)

For Intranasal Use Only
Shake Well Before Using

BRIEF SUMMARY

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, *e.g.*, joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

The use of Nasacort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Nasacort Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

PRECAUTIONS

General: In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local therapy and discontinuance of treatment with Nasacort Nasal Inhaler.

Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. Nasacort at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see CLINICAL TRIALS section).

Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances.

When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasacort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients being treated with Nasacort Nasal Inhaler should receive the following information and instructions.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Patients should use Nasacort Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations.

Carcinogenesis, Mutagenesis: Animal studies of triamcinolone acetonide to test its carcinogenic potential are underway.

Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m^2/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m^2/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m^2/day or 110 mcg/m^2/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery. Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5 - 15.0 mcg/kg/day or 20 - 110 mcg/m^2/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m^2/day and 7.0 mcg/m^2/day).

Pregnancy: Pregnancy Category C. Like other corticoids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m^2/day in the rat and 320, 640 and 1280 mcg/m^2/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m^2/day). The doses of 0.02, 0.04, 0.08, and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51, and 318.7 times the minimum recommended dose of 110 mcg of Nasacort per day and 3.2, 6.4, 12.7, and 80 times the maximum recommended dose of 440 mcg of Nasacort per day based on a patient body weight of 70 kg. Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Nasacort Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in children below the age of 12. Oral corticoids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS: In controlled and uncontrolled studies, 1257 patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed Nasacort canister. These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days).

The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received Nasacort. Nasal irritation was reported by 2.8% of the patients receiving Nasacort. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received Nasacort and included: dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects.

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).

OVERDOSAGE: Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects if the nasal application of the 15 mg of triamcinolone acetonide was administered all at once.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Please see product circular for full prescribing information.

REFERENCES:

1. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc. **2.** Ziemniak JA: Pharmacokinetics of intranasal triamcinolone acetonide. *J Respir Dis* 1991;12 (3, Suppl):S41-S42. **3.** Feiss G, Morris R, Rom D, et al: A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function. *J Allergy Clin Immunol* 1992;89:1151-1156. **4.** Findlay S, Huber F, Garcia J, et al: Efficacy of once-a-day intranasal administration of triamcinolone acetonide in patients with seasonal allergic rhinitis. *Ann Allergy* 1992;68(3):228-232.

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In Memoriam

CORRECTION

Orlando P. Johann of La Mesa, California, who died Feb 3, 1994, was misidentified in the April 1994 issue. WJM *regrets the error.*

California Medical Association

ACKERLY, ROBERT N., San Diego. Died Feb 14, 1994, aged 50. Graduate of Medical College of Virginia, Richmond, 1970. Licensed in California in 1971. Dr Ackerly was a member of the San Diego County Medical Society.

❧

ALKSNIS, HARALDS, Los Angeles. Died Feb 17, 1994, aged 81. Graduate of Latvijas Univ Med Fac, Riga, 1942. Licensed in California in 1948. Dr Alksnis was a member of the Los Angeles County Medical Association.

❧

CAMERON, JOHN R., Concord. Died Apr 15, 1994, aged 44. Graduate of Stanford University School of Medicine, Stanford, California, 1981. Licensed in California in 1982. Dr Cameron was a member of the Alameda-Contra Costa Medical Association.

❧

DURLAND, RICHARD C., Milpitas. Died Apr 26, 1994, aged 64. Graduate of University of Illinois College of Medicine, Chicago, 1959. Licensed in California in 1964. Dr Durland was a member of the Santa Clara County Medical Association.

❧

FLOCKS, MILTON, Palo Alto. Died Apr 14, 1994, aged 79. Graduate of Louisiana State University School of Medicine, New Orleans, 1940. Licensed in California in 1951. Dr Flocks was a member of the Santa Clara County Medical Association.

❧

FUNG, LUNG, Sacramento. Died Apr 1, 1994, aged 85. Graduate of Stanford University School of Medicine, Stanford, California, 1934. Licensed in California in 1934. Dr Fung was a member of the Sacramento-El Dorado Medical Society.

❧

GARRETT, ROBERT L., Vallejo. Died Apr 1, 1994, aged 85. Graduate of Washington University School of Medicine, St Louis, Missouri, 1940. Licensed in California in 1946. Dr Garrett was a member of the Solano County Medical Society.

HILL, HAROLD H., San Jose. Died May 6, 1994, aged 90. Graduate of University of Illinois College of Medicine, Chicago, 1929. Licensed in California in 1957. Dr Hill was a member of the Santa Clara County Medical Association.

❧

HILTON, BRIAN J., Berkeley. Died Apr 16, 1994, aged 78. Graduate of University of London Faculty of Medicine, London, England, 1945. Licensed in California in 1952. Dr Hilton was a member of the Alameda-Contra Costa Medical Association.

❧

HUME, JOHN V., Tracy. Died Apr 13, 1994, aged 70. Graduate of University of Colorado School of Medicine, Denver, 1953. Licensed in California in 1958. Dr Hume was a member of the San Joaquin County Medical Society.

❧

LAMB, LORIS M., Oakland. Died May 15, 1994, aged 90. Graduate of Oregon Health Sciences University, Portland, 1925. Licensed in California in 1925. Dr Lamb was a member of the Alameda-Contra Costa Medical Association.

❧

LIBBEY, JOSEPH H. Jr, Antioch. Died Mar 31, 1994, aged 84. Graduate of Stanford University School of Medicine, Stanford, California, 1938. Licensed in California in 1938. Dr Libbey was a member of the Alameda-Contra Costa Medical Association.

❧

MACCHIAGODENA, ALFREDO A., San Francisco. Died Apr 25, 1994, aged 74. Graduate of University of Bologna, 1944. Licensed in California in 1951. Dr MacChiagodena was a member of the San Francisco Medical Society.

❧

MCLAUGHLIN, BERNARD F., Burlingame. Died Apr 9, 1994, aged 79. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1940. Licensed in California in 1946. Dr McLaughlin was a member of the San Mateo County Medical Association.

❧

MASON, JAMES K., Ventura. Died Apr 18, 1994, aged 58. Graduate of George Washington University School of Medicine, Washington, DC, 1961. Licensed in California in 1963. Dr Mason was a member of the Ventura County Medical Society.

MASON, RICHARD P., Fortuna. Died Apr 20, 1994, aged 67. Graduate of Loma Linda University School of Medicine, 1956. Licensed in California in 1958. Dr Mason was a member of the Humboldt-Del Norte Medical Society.

❧

PERKINS, HERMAN B., Vallejo. Died Apr 23, 1994, aged 90. Graduate of University of Cincinnati, Cincinnati, Ohio, 1934. Licensed in California in 1934. Dr Perkins was a member of the Solano County Medical Society,

❧

PRIDAY, SIDNEY M., Oakland. Died Mar 22, 1994, aged 75. Graduate of University of Utah School of Medicine, Salt Lake City, 1945. Licensed in California in 1948. Dr Priday was a member of the Alameda-Contra Costa Medical Association.

❧

RECTOR, E. WILLIAM, Sacramento. Died Mar 30, 1994, aged 81. Graduate of McGill University Faculty of Medicine, Montreal, 1938. Licensed in California in 1939. Dr Rector was a member of the Sacramento-El Dorado Medical Society.

❧

SCHIFF, MAURICE, Rancho Santa Fe. Died Apr 1994, aged 73. Graduate of Boston University School of Medicine, Boston, Massachusetts, 1942. Licensed in California in 1952. Dr Schiff was a member of the San Diego County Medical Society.

❧

TAYLOR, EDWIN M., Oakland. Died Apr 25, 1994, aged 95. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1923. Dr Taylor was a member of the Alameda-Contra Costa Medical Association.

❧

WALLACE, ARTHUR F., Sacramento. Died Mar 31, 1994, aged 84. Graduate of St Louis University School of Medicine, St Louis, Missouri, 1935. Licensed in California in 1936. Dr Wallace was a member of the Sacramento-El Dorado Medical Society.

Denver Medical Society

ABERNATHY, CHARLES MEREDITH Jr. Died Mar 24, 1994, aged 53. Graduate of Northwestern University Medical School, Chicago, Illinois, 1966. Licensed in Colorado in 1967.

Continuing Medical Education

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

July 29-30—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

August 19-20—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

September 10-11—**5th Annual Pulmonary and Infectious Diseases Seminar: September in Sedona.** Mayo Clinic-Scottsdale at Los Abrigados Resort, Sedona. Sat-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

September 25-29—**44th Annual Southwest OB/GYN Meeting.** Southwest OB/GYN Society at Loews Ventana Canyon Resort, Tucson. Sun-Thurs. Contact: Jay Epstein, MD, (602) 678-1111.

October 7-8—**Clinical Assessment in Today's World of Medicine for Nurses.** Mayo Clinic-Scottsdale at Ashton B. Taylor Auditorium, Scottsdale. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

October 14-15—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Doubletree Hotel, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

October 21-22—**Parkinson's Disease and Movement Disorders for the Practitioner.** Mayo Clinic-Scottsdale at Ritz-Carlton Hotel, Phoenix. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

October 28-30—**Arrthymias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Camelback Inn, Scottsdale. Fri-Sun. Contact: Karen DeBont, (800) 421-3756.

November 4-5—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

November 4-5—**Hematology and Oncology for Primary Care Physicians.** Mayo Clinic-Scottsdale at the Orange Tree Golf Resort, Scottsdale. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

November 7-11—**The Physician Management Seminar Series: Seminar I.** American College of Physician Executives at the Scottsdale Plaza Resort, Scottsdale. Mon-Fri. Contact: (800) 562-8088.

November 7-11—**The Physician Management Seminar Series: Seminar II.** American College of Physician Executives at the Scottsdale Plaza Resort, Scottsdale. Mon-Fri. Contact: (800) 562-8088.

November 10-12—**7th Annual Techniques in Gynecologic Surgery.** Mayo Clinic-Scottsdale at Marriott's Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

November 17-19—**Pediatric Orthopaedics: A Comprehensive Course.** American Academy of Orthopaedic Surgeons at The Pointe Hilton Resort at Squaw Peak, Phoenix. Thurs-Sat. Contact: AAOS, (708) 823-7186.

December 2-3—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

December 2-4—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Hyatt Regency, Scottsdale. Fri-Sun. Contact: Karen DeBont, (800) 421-3756.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

November 11-13—**Anesthesiology Update: 1994.** UCD at Monterey Plaza, Monterey. Fri-Sun. 14 hrs. $325. Contact: UCD.

November 18-19—**4th Annual Pain Conference.** UCD at Inn at Napa Valley. Fri-Sat. 11 hrs. $300. Contact: UCD.

CARDIOLOGY

July 22-24—**Coronary Heart Disease.** American College of Emergency Physicians at Marriott Tenaya, Yosemite. Fri-Sun. 11 hrs. Contact: Karen DeBont, Meetings Coordinator, 1500 W Canal Ct, Ste #500, Littleton, CO 80120-4528. (800) 421-3756.

July 24-28—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. 19 hrs. Contact: UCD.

August 4-6—**Critical Care Cardiology.** American College of Cardiology at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 17 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

September 10—**Primary Care Issues in Cardiac and Vascular Disease.** Alta Bates Medical Center at Claremont Resort, Berkeley. Sat. Contact: Caroline Carey, Alta Bates Med Ctr, (510) 204-3884.

September 23-24—**Arrhythmias: Interpretation, Diagnosis, and Management.** American College of Emergency Physicians at Desert Inn, Las Vegas, NV. Fri-Sat. 11 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

October 13-15—**Cardiology Update: 1994.** UCSF at Carmel Valley Resort, Carmel. Thurs-Sat. 18 hrs. Contact: UCSF.

October 27-30—**East Visits West: Coronary Interventions 1994.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sun. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, 403C, La Jolla 92037. (619) 554-8556.

November 18-20—**Arrhythmias: Interpretation, Diagnosis, and Management.** American College of Emergency Physicians at Disneyland Hotel, Anaheim. Fri-Sun. 11 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

DERMATOLOGY

July 19-23—**11th Annual Superficial Anatomy and Cutaneous Surgery.** UCSD and Scripps Clinic at La Jolla. Tues-Sat. 33 hrs. $1100. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037 (619) 554-8556.

August 8-10—**Dermatology for the Non-Dermatologists.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 28-31—**Advanced Seminars in Dermatology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Wed. Contact: UCD.

EMERGENCY MEDICINE

July 19-20—**5th Annual High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians at Pan Pacific Hotel, San Francisco. Tues-Wed. 15 hrs. $450-$495. Contact: Alpen Travel and Meeting, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 451-RISK (7475).

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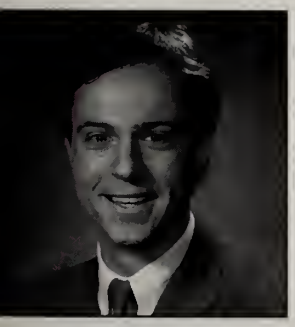

Tim Hutsko
Phoenix, Arizona

Rob Battenschlag
Seattle, Washington

Tony Ochoa
Vancouver, Washington

Robert Posch
Seattle, Washington

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Dr Mangano is Vice Chair and Professor, Department of Anesthesia, and Director of the Multicenter Study of Perioperative Ischemia Research Group, University of California, San Francisco, School of Medicine.

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★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 12)

July 29—**ACLS Recertification.** CPR Seminars at San Francisco. Fri. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro 94577. (510) 632-6135.

August 15-19—**Emergency Medicine Symposium II.** UCSD at Basic Science Building. Mon-Fri. 32 hrs. $495. Contact: UCSD.

September 10-11—**ACLS Provider.** CPR Seminars at Antioch. Sat-Sun. CPR Seminars, 1933 Davis St, Ste 297, San Leandro 94577. (510) 632-6135.

September 16—**Advanced Burn Life Support Course.** Torrance Memorial Burn Center at Torrance Memorial Hospital. Fri. 9 hrs. $220. Contact: Nancy Wise, (310) 517-4605.

September 17—**ACLS Recertification.** CPR Seminars at San Francisco. Fri. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro 94577. (510) 632-6135.

September 25-29—**West Coast Emergency Medicine Review Course.** American College of Emergency Physicians and the Emergency Physicians' Medical Group at San Francisco. Sun-Thurs. Contact: EPMG, 1 Montgomery St, Ste 1360, San Francisco 94104. (800) 436-7277.

October 14-16—**Advances in Emergency Medicine.** Continuing Medical Associates at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 17-21—**Emergency Medicine Symposium.** UCSD at San Diego Hilton. Mon-Fri. 17 hrs. $475. Contact: UCSD.

November 7-11—**Emergency Medicine Symposium.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

December 4-9—**15th Annual Conference: Current Concepts in Emergency Care.** American College of Emergency Physicians at Maui Intercontinental Resort, Hawaii. Sun-Fri. 20 hrs. Contact: Kailani World Travel, 4192 Meridian Ave, Box 9751, Bellingham, WA 98227. (800) 544-9269 or (206) 671-1800.

December 12-16—**Emergency Medicine Symposium.** UCSD at Basic Science Building. Mon-Fri. 32 hrs. $495. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

August 5-7—**Cardiology for the Family Physician and Internist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 19-21—**Office Gynecology for the Primary Care Physician.** San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 19-21—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Le Meridien, San Diego. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

August 21-26—**Essentials of Primary Care: A Core Curriculum for Practice in the 1990s.** UCSF at Resort Squaw Creek, Olympic Valley, North Lake Tahoe. Sun-Fri. 25 hrs. $545. Contact: UCSF.

November 5—**Neurology for Primary Care.** UCD at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. $95. Contact: UCD.

December 9-11—**Neurology for the Non-Neurologist.** American College of Emergency Physicians at Desert Inn, Las Vegas, Nevada. Fri-Sun. 12 hrs. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

1994—**HIV Primary Care Mini-Residency.** UCSD at Owen Clinic, San Diego. Ongoing. 30 hrs. Contact: UCSD.

GERIATRICS

October 7-8—**Coming of Age: Geriatrics for the Primary Care Provider—Part II.** UCD at Sacramento Inn. Fri-Sat. 13 hrs. $235. Contact: UCD.

November 7-9—**Geriatrics Update: 1994.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Mon-Wed. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

1994—**Mini-residency in Geriatrics.** UCSD at Multi Purpose Facility, San Diego. Ongoing. 40-80 hrs. $195. Contact: UCSD.

1994—**The GGG/Alzheimer's Family Center: Sharing the Caring—Training Series on Dementia.** UCSD. Ongoing. 4 hrs. $25. Contact: UCSD.

INFECTIOUS DISEASE

November 4-6—**Advances in Infectious Disease.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

August 14-19—**11th Annual New Advances in Internal Medicine.** UCD at Hyatt Monterey. Sun-Fri. Contact: UCD.

August 26-September 1—**Comprehensive Nephrology Review Course.** UCLA School of Medicine at Beverly Hilton Hotel, Beverly Hills. Fri-Thurs. 51 hrs. $895. Contact: UCLA.

September 17-19—**1994 International Symposium on Bone Marrow Transplantation.** Sutter Community Hospital at Fairmont Hotel, San Francisco. Sat-Mon. Contact: Sutter Community, 2800 L St, Sacramento 95816. (800) 777-0231.

October 1—**Focus on Venous Access: Hemodialysis, Pheresos, Chemoinfusion.** UCSD at Le Meridien Hotel, Newport Beach. Sat. 8 hrs. $125. Contact: UCSD.

October 22—**Diabetes.** Sutter Community Hospitals at Sacramento. Sat. Contact: Peggy Coit, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

OB/GYN

October 1—**Colscopy.** Sutter Community Hospitals at Sacramento. Sat. Contacat: Lynne MacRae, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

October 1-2—**6th Annual Ultrasound Update: 1994.** UCD at Red Lion Inn, Sacramento. Sat-Sun. 10 hrs. $240. Contact: UCD.

October 8—**Women's Health.** Sutter Community Hospitals at Stockton. Sat. Contact: Catherine Davis, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

December 1-3—**Obstetrics and Gynecology Conference.** University of Nebraska Medical Center at Bally's, Las Vegas, Nevada. Thurs-Sat. $275. Contact: UNMC, 600 S 42nd St, Omaha, NE 68198-5651. (800) 642-1095 or (402) 559-4152.

OCCUPATIONAL/ENVIRONMENTAL

July 25-29—**8th Annual Sports Medicine.** UCSD at San Diego Princess Resort. Mon-Fri. 20 hrs. $395. Contact: UCSD.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs, (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

(Continued on Page 22)

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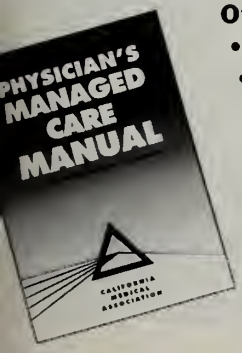

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The Swallowing Center

At the Swallowing Center at USC University Hospital, advanced diagnostic capabilities allow specialists to determine if patients with reflux disease are benefiting from medication, or if surgical interventions would be more appropriate. By receiving an accurate diagnosis in a timely fashion, patients may avoid the ravages of end-stage disease that have been associated with long-term medication.

Sophisticated Diagnoses

Patients at the Center undergo a comprehensive history and physical examination, and a series of sophisticated diagnostic evaluations. These may include esophageal manometry, video esophagram, nasopharyngeal and esophageal endoscopy, quantitative radionuclide gastric and esophageal scanning, and ambulatory motility, 24-hour pH, bile probe, and gastric emptying tests.

Esophageal manometry measures and records the muscle function of the esophagus. These studies are particularly detailed at the Swallowing Center, allowing for easy identification of abnormalities. Video esophagrams are used to visually assess the oropharyngeal, pharyngoesophageal and esophageal phases of swallowing. With this test, specialists see each swallowing motion as it occurs.

Multidisciplinary Approach to Swallowing Problems

This diagnostic expertise represents one of the many unique strengths that distinguishes the Swallowing Center at USC University Hospital. Another strength is its multidisciplinary approach: The Center's specialists include gastroenterologists, neurologists, general surgeons, otolaryngologists, pathologists, speech pathologists, radiologists and thoracic specialists.

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Treating Swallowing Disorders

The Swallowing Center evaluates and treats the full spectrum of swallowing disorders, including gastroesophageal reflux, esophageal strictures, diverticular of the esophagus, gastroparesis and scleroderma. Patients are referred for evaluation and treatment of:

- reflux disease refractory to medical therapy,
- symptoms whose etiology cannot be identified,
- swallowing disorders caused by neurologic dysfunction, Zencker's diverticulum or cricopharyngeal muscle dysfunction.

The Center has a particular interest in Barrett's esophagus, duodenal gastric reflux and complicated re-operations.

Innovative Surgical Approaches

The Center offers innovative treatment options to those patients with reflux disease or abnormalities of the peristaltic muscular contractions of the esophagus. These include balloon dilation and esophageal myotomy in which the muscular wall of the esophagus is divided, reducing the strength of esophageal contractions and turning swallowing into a gravity system.

The Nissen fundoplication procedure is done for patients with a defective lower esophageal sphincter through which acid gastric juice regurgitates. In this procedure, the surgeon augments the lower esophageal sphincter function by using the stomach muscle to reconstruct a new sphincter. The Center is also involved in endoscopic antireflux repair, utilizing scopes inserted into the inflated stomach orally and transcutaneously.

Close Contact With Referring Physicians

Specialists at the Swallowing Center are dedicated to maintaining close contact and frequent communication with referring physicians throughout the United States.

The Swallowing Center Co-Directors

Tom R. DeMeester, M.D., professor and chairman, Department of Surgery at the University of Southern California School of Medicine, earned his medical degree from the University of Michigan, Ann Arbor, and received his surgical training at The Johns Hopkins Hospital in Baltimore. After a tour of military duty, Dr. DeMeester joined the faculty of the University of Chicago as Chief of Thoracic Surgery, a position he held for 10 years. He then served as Chairman of Surgery at Creighton University School of Medicine in Omaha, Nebraska. Dr. DeMeester joined USC in 1990.

Cedric G. Bremner, M.D., professor of Clinical Surgery and director of Clinical Research at USC, received his medical training at the University of the Witwatersrand in Johannesburg, South Africa, and spent five years at the Royal Postgraduate Medical School and the Hammersmith Hospital in London doing postgraduate studies. He also did his F.R.C.S. in England and Edinburgh, Scotland before returning to Johannesburg and becoming a staff member of the University Medical School. He spent a year at the Mayo Clinic and in 1979 was promoted to full professor of the University of Johannesburg. He joined USC in 1993.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 18)

September 22-25—**Emerging Issues in Occupational and Environmental Health.** American College of Occupational and Environmental Medicine and the Western Occupational and Environmental Medical Association at Stouffer Stanford Court Hotel, San Francisco. Thurs-Sun. Contact: WOEMA, 50 First St, Ste 300, San Francisco 94105. (415) 764-4803.

ONCOLOGY

July 19-22—**Pan Pacific Lymphoma Conference.** University of Nebraska Medical Center at Ritz-Carlton-Mauna Lani, Kohala Coast, Hawaii. Tues-Fri. Contact: UNMC, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152.

September 25-27—**State of Breast Cancer 1994: An Interactive Symposium.** UCSF at Sheraton Palace Hotel, San Francisco. Sun-Tues. 20 hrs. $350. Contact: UCSF.

October 6-8—**18th Annual Physicians Cancer Symposium.** Scripps Memorial Hospital at Stevens Cancer Center, San Diego. Thurs-Sat. 16.5 hrs. $390. Contact: Cancer Symposium, 2603 Main St, Ste 690, Irvine 92714. (800) 321-6338.

ORTHOPEDICS

July 15-16—**Hand Review 1994.** UCD at Holiday Inn, Capitol Plaza, Sacramento. Fri-Sat. $275. Contact: UCD.

July 23-30—**Update in Orthopaedics '94.** Kaiser Permanente Medical Center, South San Francisco at Hyatt Regency, Maui, Hawaii. Sat-Sat. 18 hrs. $425. Contact: Jerry VanMeter, MD, 1200 El Camino Real, So San Francisco 94080. (415) 742-2461.

August 13-17—**58th Annual Meeting Western Orthopedic Association at Long Beach.** Sat-Wed. 18 hrs. Contact: H. J. Martin, (510) 671-2164.

1994—**Educational Program for Musculoskeletal Evaluation and Rehabilitation.** UCSD at La Jolla. 35.5 hrs. $500. Contact: UCSD.

OTOLARYNGOLOGY

September 11-16–October 9-14—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 53 hrs. $875-$1,100. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

November 3-5—**Otolaryngology Update: 1994.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17 hrs. $425. Contact: UCSF.

PATHOLOGY

August 13-20—**15th Annual Comprehensive Fine Needle Biopsy Course.** UCSF at Ritz-Carlton Mauni Lani, Big Island of Hawaii. Sat-Sat. 27 hrs. $950. Contact: UCSF.

August 24-27—**Centennial Conference on Coccidioidomycosis.** Stanford University at University Campus. Wed-Sat. Contact: Complete Conference Management, 1660 Hotel Circle North, #220, San Diego 92108. (619) 299-6673.

September 17—**34th Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at La Jolla Marriott. Sat. Contact: National Kidney Foundation, 5777 W. Century Blvd, Ste 395, Los Angeles 90045-7404. (310) 641-8152.

September 17-21—**9th Combined Skin Pathology Course and 5th Annual Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Sat-Wed. 40 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

July 15-17—**2nd Annual Pediatric Update.** Stanford University School of Medicine at Lucile Packard Children's Hospital, Palo Alto. Fri-Sun. Contact: Elinor Meyer, Medical Outreach Dept, 725 Welch Rd, Palo Alto 94304. (415) 497-8554.

August 22-24—**Pediatrics Update 1994.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 1—**Therapy for Childhood Neuromuscular Diseases.** Children's Hospital and Health Center at Hyatt Regency, San Diego. Sat. 6.5 hrs. $75. Contact: CAM, 3030 Children's Way, San Diego 92123. (619) 576-5819.

October 22—**Pediatrics.** Sutter Community Hospitals at Auburn. Sat. Contact: Lynne MacRae, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

October 29—**Ambulatory Pediatrics.** UCD at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. $95. Contact: UCD.

December 1-4—**Society of ENT Advances in Children.** UCD at Radisson Hotel, Sacramento. Thurs-Sun. 10 hrs. Contact: UCD.

December 3—**13th Annual Binational Pediatric Conference.** Children's Hospital San Diego and American Academy of Pediatrics at Mercy Hospital Educational Center, San Diego. Sat. $45. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

PHYSICAL MEDICINE/REHABILITATION

August 11-13—**2nd Annual Clinical Exercise, Physiology and Cardiac Rehabilitation Conference.** American College of Cardiology at Holiday Inn, Palo Alto. Thurs-Sat. 21 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

October 8-12—**56th Annual Assembly, American Academy of Physical Medicine and Rehabilitation** at Anaheim Hilton Hotel and Towers and Anaheim Convention Center. Sun-Wed. Contact: AAPMR, 122 S Michigan Ave, Ste 1300, Chicago, IL 60603-6107. (312) 922-9366.

PSYCHIATRY

September 30-October 4—**Power of the Art: Introduction to Medical Hypnosis and Other Practical Wisdoms.** UCSD at Sheridan Grande, San Diego. Fri-Tues. 26 hrs. $550. Contact: UCSD.

October 7-11—**The Power of the Art: Introduction to Medical Hypnosis and Other Practical Wisdoms.** UCSD at Colonial Inn, La Jolla. Fri-Tues. 26 hrs. Contact: UCSD.

October 14-15—**Psychopharmacology Clinical Research Update.** UCD at Hilton Hotel, San Francisco. Fri-Sat. 14 hrs. $395. Contact: UCD.

1994—**Basic Clinical Hypnosis Training.** UCSD at La Jolla. Ongoing. 30 hrs. $245. Contact: UCSD.

PULMONARY MEDICINE

August 12-14—**Diagnosis and Management of Respiratory Diseases.** American College of Emergency Physicians at Hyatt Regency, Lake Tahoe, Nevada. Fri-Sun. 12 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

September 23-25—**Diagnosis and Management of Respiratory Diseases.** American College of Emergency Physicians at Esmeralda Resort, Palm Springs. Fri-Sun. 12 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

October 13-15—**Pulmonary and Critical Care Medicine.** UCSF at Ana Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

RADIOLOGY

August 25-28—**Physics of Diagnostic Radiology.** UCD on Campus. Thurs-Sun. Contact: UCD.

September 8-10—**Trauma and Emergency Radiology.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 16 hrs. $395. Contact: UCSF.

September 29–October 1—**Interventional Hepatobiliary Radiology.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 18 hrs. $550. Contact: UCSF.

October 2—**Oncologic Imaging Update.** UCSF at Fairmont Hotel, San Francisco. Sun. 6.5 hrs. $150. Contact: UCSF.

October 3-7—**Clinical Magnetic Resonance Imaging.** UCSF at Fairmont Hotel, San Francisco. Mon-Fri. 33 hrs. $595. Contact: UCSF.

October 7-8—**Vascular Ultrasound: State of the Art.** UCSF at Fairmont Hotel, San Francisco. Fri-Sat. 13.5 hrs. $295. Contact: UCSF.

October 10-14—**Neuroimaging Visiting Fellowship Program.** Stanford School of Medicine. Mon-Fri. 40 hrs. Contact: Barbara Platt, (415) 723-4733.

October 10-16—**Advanced Imaging of the Musculoskeletal System With Emphasis on MRI.** UCSD at Hotel del Coronado, San Diego. Mon-Sun. Contact: UCSD.

October 17-19—**Radiology for the Non-Radiologist.** UCSD at Hyatt Regency, La Jolla. Mon-Wed. 20 hrs. $450. Contact: UCSD.

October 17-21—**19th Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. Contact: UCSD.

October 21-23—**14th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. Contact: UCSD.

October 31–November 4—**Diagnostic Radiology Seminars.** UCSF at Ritz-Carlton Kapalua, Maui, Hawaii. Mon-Fri. 26 hrs. $595. Contact: UCSF.

(Continued on Page 23)

INTENSIVE CME IN EXTENSIVE LOCATIONS

MONTH	CORONARY HEART DISEASE UPDATE	ARRHYTHMIAS: INTERPRETATION, DIAGNOSIS AND MANAGEMENT	DIAGNOSIS AND MANAGEMENT OF RESPIRATORY DISEASES	NEUROLOGY FOR THE NON-NEUROLOGIST
Aug 94	Nantucket, MA 19-21	Lake Louise, Canada 5-7	Lake Tahoe, NV 12-14	Lake George, NY 19-21
Sept. 94	Key West, FL 30-10/2	Las Vegas, NV 23-24	Palm Springs, CA 23-25	Bermuda 29-10/1
Oct. 94	Las Vegas, NV 7-9	Scottsdale, AZ 28-30	Orlando, FL 7-9	Cabo San Lucas, Mex. 20-22
Nov. 94	Orlando, FL 18-20	Anaheim,CA 18-20	St. John, USVI 17-19	Naples, FL 4-6
Dec. 94	Grand Cayman Isl. 1-3	Key West, FL 2-4	Scottsdale, AZ 2-4	Las Vegas, NV 9-11
Feb. 95	Scottsdale, AZ 24-26	Breckenridge, CO 19-21	Las Vegas, NV 3-5	Key West, FL 17-19
Mar. 95	Las Vegas 24-26	Grand Cayman Isl. 3/30-4/1	Orlando, FL 3/31-4/2	Squaw Valley, CA 9-11

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CONTINUING MEDICAL EDUCATION

(Continued from Page 22)

November 14-18—**A Practical Approach to Breast Imaging.** UCSF at Ritz-Carlton, Rancho Mirage. Mon-Fri. 20 hrs. $595. Contact: UCSF.

1994—**Fellowship in Interventional Radiology for Radiologists.** UCSD Medical Center. Ongoing. 40 hrs. $700. Contact: UCSD.

1994—**Visiting Fellowship in Magnetic Resonance Imaging.** UCSD at MR Institute, San Diego. Ongoing. 40 hrs. $1,200. Contact: UCSD.

1994—**Visiting Fellowship for Physicians and Sonographers in Duplex Ultrasound: Focus on Carotid and Deep Venous Thrombosis.** Ongoing. 30 hrs. $600. Contact: UCSD.

1994—**Visiting Fellowship Program of Endovaginal Sonography: Focus on Techniques and Application.** UCSD Medical Center. Monthly. 30 hrs. $600. Contact: UCSD.

SURGERY

September 9-13—**Summer Institute—Intensive Surgical Skills.** American Academy of Orthopedic Surgeons at Monterey Conference Center, Marriott Hotel and Doubletree Hotel, Monterey. Fri-Tues. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

October 29—**Suture Workshop.** Sutter Community Hospitals at Sacramento. Sat. Contact: Catherine Davis, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

GENERAL/MULTIDISCIPLINARY

October 27-30—**1994 CME/Golf Meeting.** Nevada Academy of Family Physicians at Sheraton Desert Inn Hotel & Casino, Las Vegas. Thurs-Sun. 21 hrs. Contact: Barbara Bolling, NAFP, PO Box 27713, Las Vegas, NV 89126-1713. (702) 647-0117.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

July 25-29—**21st Annual Renal Disease Program: Renal Disease and Electrolyte Disorders.** University of Colorado Health Sciences Center at The Given Biomedical Institute, Aspen. Mon-Fri. Contact: U of Colo.

July 31-August 3—**Third Biannual Type 1 Diabetes Program: Management of Pediatric Diabetes.** University of Colorado Health Sciences Center at Keystone. Sun-Wed. Contact: U of Colo.

July 31-August 3—**Cardiovascular Interventions: Technology at the Summit, IV.** University of Colorado Health Sciences Center at Aspen. Sun-Wed. Contact: U of Colo.

August 1-5—**Dynamic Psychotherapy Program.** University of Colorado Health Sciences Center at Aspen. Mon-Fri. Contact: U of Colo.

August 7-11—**37th Annual Pediatric Program.** Children's Hospital and University of Colorado Health Sciences Center at The Given Biomedical Institute, Aspen. Sun-Thurs. Contact: U of Colo.

August 7-12—**19th Annual Primary Musculoskeletal Care Program.** University of Colorado Health Sciences Center at Breckenridge. Sun-Fri. Contact: U of Colo.

August 8-12—**12th Annual Pediatric Infectious Disease Conference.** Children's Hospital at Aspen. Mon-Fri. Contact: Kim Brenckle, Children's Hospital, 1056 E 19th Ave, Box 055, Denver. (303) 861-6981.

(Continued on Page 24)

(Continued from Page 23)

August 11-13—**Pediatric Cardiology: The Failing Heart.** University of Colorado School of Medicine at The Given Biomedical Institute, Aspen. Wed-Sat. Contact: U of Colo.

August 11-14—**Fourth Annual Conference: Women Physicians/Finding a Balance.** Rose Medical Center at Breckenridge Hilton Hotel. Thurs-Sun. Contact: Women Physicians Conference, 9101 E Kenyon Ave, #3000, Denver 80237. (303) 770-2220; FAX (303) 770-1812.

August 11-14—**Multimodality Approaches to Limb Salvage for Extremity Sarcoma.** P/SL Swedish Healthcare System at Westin Resort, Vail. Thurs-Sun. Contact: P/SL CME Office, (800) 633-6824.

August 14-17—**Fourth National Kaiser Permanente Emergency Medicine Conference.** Colorado Medical Society and Colorado Permanente Medical Group at Beavercreek. Contact: KPEM 94, PO Box 7131, Corte Madera, CA 94976-7131. (415) 927-7450.

August 15-20—**Breast Imaging and Intervention Into the 21st Century.** Radiology Imaging Associates at Broadmoor Hotel, Colorado Springs. Sun-Fri. Contact: Ryals & Associates, (404) 641-9773.

August 17-19—**Genetic Therapy.** University of Colorado Health Sciences Center at Aspen. Wed-Sat. Contact: U of Colo.

August 17-20—**4th Annual Musculoskeletal Infection Meeting.** University of Colorado Health Sciences Center at Snowmass Village. Wed-Sun. Contact: U of Colo.

September 16-18—**Sixth National Conference on Outreach Education: The Changing Colors of Outreach Education.** University of Colorado Health Sciences Center at Tamarron Resort, Durango. Fri-Sun. Contact: U of Colo.

September 16-18—**Third Annual Medical Ethics Conference.** University of Colorado Health Sciences Center at Aspen. Fri-Sun. Contact: U of Colo.

September 30—**Rocky Mountain Regional Cardiovascular Disease Conference.** University of Colorado Health Sciences Center at Vail. Fri. Contact: U of Colo.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

Every Friday (except 4th Friday of month)—**Various Topics in Contemporary Medicine (Midday CME Series).** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 270-6761.

IDAHO

July 28-30—**Idaho Medical Association—Annual Meeting.** Sun Valley. Wed-Fri. Contact: IMA, 305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 18-22—**Imaging 1994.** Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 22-24—**Arrhythmias, Diagnosis and Treatment.** Eldorado Hotel, Santa Fe. Fri-Sun. Contact: Tracy L. Green, New Mexico Heart Clinic, (505) 841-1000.

August 7-11—**Lovelace Santa Fe Neurology 1994.** Eldorado Hotel, Santa Fe. Contact: Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 16-17—**Annual Meeting—American College of Surgeons, New Mexico Chapter.** Hotel de Santa Fe, Santa Fe. Contact: Bonnie Smith, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237.

September 17—**Management of Patient with Cardiac Disease.** Journal Center, Albuquerque. Sat. Contact: Tracy L. Green, New Mexico Heart Clinic, (505) 841-1000.

October 5-9—**3rd Annual New Mexico Medical Computer Course.** Holiday Inn Pyramid Hotel, Albuquerque. Contact: Floyd Smith, NMOMA, PO Box 90396, Albuquerque 87199-0396. (505) 828-1905.

October 8-9—**What Is New With the Newborn?** New Mexico Pediatric Society at Snakedance, Taos Ski Valley. Contact: Richard Rolston, MD, (505) 898-7898.

October 28-29—**ECG Interpretation for the Primary Care Physician.** Journal Center, Albuquerque. Fri-Sun. Contact: Tracy L. Green, New Mexico Heart Clinic, (505) 841-1000.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

September 21-24—**Utah Medical Association—Annual Meeting.** University Park Hotel, Salt Lake City. Wed-Sat. Contact: Utah Medical Association.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

(Continued on Page 25)

CONTINUING MEDICAL EDUCATION

(Continued from Page 24)

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

July 29-30—**From Bench to Bedside: A State of the Art HIV Conference for Primary Care Providers.** Seattle. Fri-Sat. Contact: U/W.

July 29-30—**Orthopaedic Trauma Update.** Seattle. Fri-Sat. Contact: U/W.

August 4-6—**Breast Cancer in Young Women.** Seattle. Thurs-Sat. Contact: U/W.

August 8-13—**Summer Seminar in Health Care Ethics.** Seattle. Mon-Sat. Contact: U/W.

September 9—**Interventional Radiology.** Seattle. Fri. Contact: U/W.

September 9-11—**Radiation Health Effects and Hanford: A Joint Conference for Concerned Citizens and Health Care Providers.** Spokane. Fri-Sun. Contact: U/W.

September 10-11—**Pediatric Advanced Life Support.** Seattle. Sat-Sun. Contact: Children's, (206) 368-4802.

September 11-16—**North Pacific Pediatric Society—149th Meeting.** Blaine. Sun-Fri. Contact: Norma Brooks, (206) 248-2229.

September 19-23—**Annual Advances in Family Practice.** Seattle. Mon-Fri. Contact: U/W.

September 29-30—**New Approaches to Common Urinary Tract Problems in Children.** Seattle. Thurs-Fri. Contact: Children's, (206) 526-2501.

October 15—**Arthrocentesis & Injection Techniques.** Seattle. Sat. Contact: U/W.

(Continued on Page 98)

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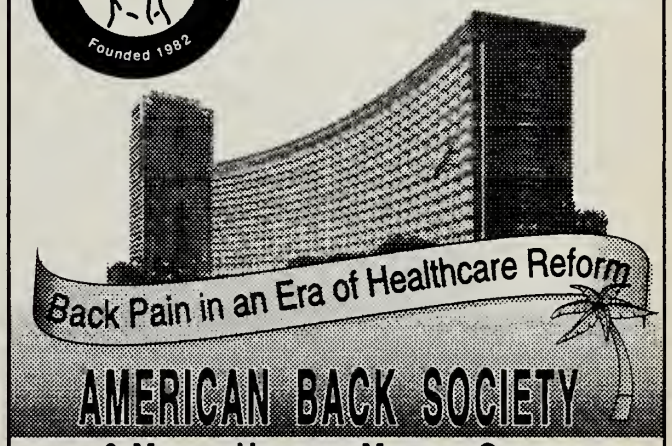


& MIDWAY HOSPITAL MEDICAL CENTER

in association with Comprehensive Spine Center of Midway Hospital, & Center for Comprehensive Rehabilitation of Los Angeles.

Program Committee: Rene Cailliet, M.D.; Philip Greenman, D.O.; Clive M. Segil, M.D., F.R.C.S.(C), F.A.C.S.; Edward H. Simmons, M.D., B.Sc.(Med.), F.R.C.S.(C)

Local Host Committee: Clive M. Segil, M.D., F.R.C.S.(C), F.A.C.S.; Michael Shapow, P.T.

For information contact Aubrey Swartz, M.D., American Back Society, 2647 E. 14th St., Suite 401, Oakland, CA 94601. Tel (510) 536-9929 • Fax (510) 536-1812.

CONTINUING MEDICAL EDUCATION CALENDAR

The Southern Medical Association is accredited by the Accreditation Council for Continuing Medical Education to sponso continuing medical education for physicians.

JULY 18-21, 1994

FOCUS ON THE FEMALE PATIENT
LOCATION: Kiawah Island Resort, SC
SPECIALTY: OB/Gyn, Primary Care
CME CREDIT: AMA Category 1
FEE: SMA Members $350; Non-Members $475; Non-Physicians $225

JULY 22-24, 1994

FOCUS ON THE MALE PATIENT
LOCATION: Kiawah Island Resort, SC
SPECIALTY: Primary Care
CME CREDIT: AMA Category 1
FEE: SMA Member $310; Non-member $435; Non-Physician $225

JULY 24-27, 1994

GENERAL SURGERY
LOCATION: Sea Island, Georgia
SPECIALTY: Surgery
CME CREDIT: AMA Category 1
FEE: SMA Member $475; Non-member $600; Non-Physician $300

JULY 28-30, 1994

SOUTHERN ASSOCIATION FOR ONCOLOGY ANNUAL MEETING
LOCATION: Jekyll Island, Georgia
SPECIALTY: Oncology
CME CREDIT: AMA Category 1
FEE: SAO Member $400; Non-member $550

JULY 29-31, 1994

PEDIATRICS AND ADOLESCENT MEDICINE
LOCATION: Sea Island, Georgia
SPECIALTY: Primary Care
CME CREDIT: AMA Category 1 - 15 hours
AAFP Prescribed - 15 hours
AOA Category 2-A - 15 hours
FEE: SMA Member $310; Non-member $435; Non Physician $225

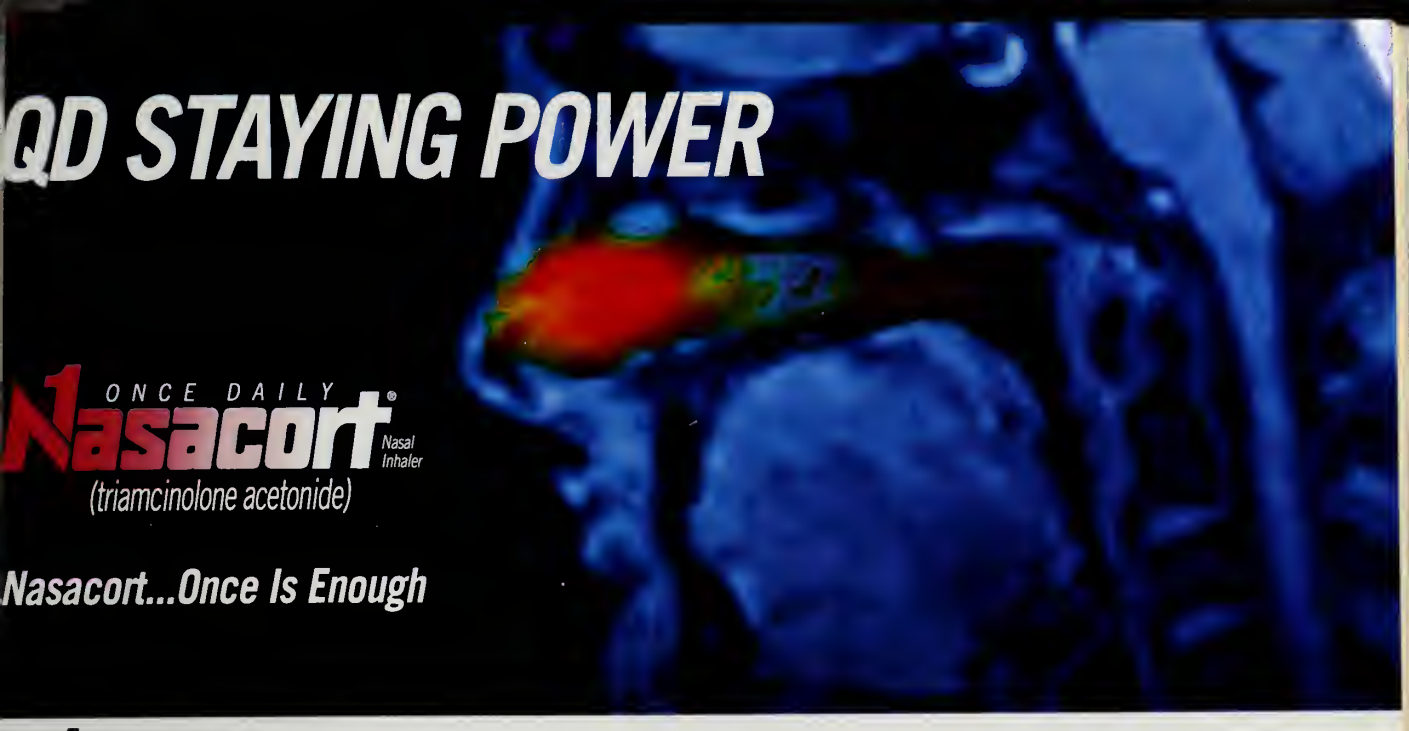
AUGUST 12-14, 1994

MUSCULOSKELETAL PROBLEMS IN PRIMARY CARE
LOCATION: Naples, Florida
SPECIALTY: Primary Care
CME CREDIT: AMA Category 1
FEE: SMA Member $295; Non-member $420; Non-Physician $200

AUGUST 19-21, 1994

SOUTHERN ORTHOPAEDIC ASSOCIATION ANNUAL MEETING
LOCATION: Bermuda
SPECIALTY: Orthopaedic and Traumatic Surgery
CME CREDIT: AMA Category 1
FEE: SOA Member $400; Non-member $550

For more information, call Michelle Williamson, Southern Medical Association, 800-423-4992 or 205-945-1840—TODAY!



ONCE DAILY
Nasacort® Nasal Inhaler
(triamcinolone acetonide)

For Intranasal Use Only
Shake Well Before Using

BRIEF SUMMARY

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, *e.g.*, joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

The use of Nasacort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Nasacort Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

PRECAUTIONS

General: In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local therapy and discontinuance of treatment with Nasacort Nasal Inhaler.

Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. Nasacort at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see CLINICAL TRIALS section).

Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances.

When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasacort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients being treated with Nasacort Nasal Inhaler should receive the following information and instructions.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Patients should use Nasacort Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations.

Carcinogenesis, Mutagenesis: Animal studies of triamcinolone acetonide to test its carcinogenic potential are underway.

Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m^2/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m^2/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m^2/day or 110 mcg/m^2/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery. Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5 - 15.0 mcg/kg/day or 20 - 110 mcg/m^2/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m^2/day and 7.0 mcg/m^2/day).

Pregnancy: Pregnancy Category C. Like other corticoids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m^2/day in the rat and 320, 640 and 1280 mcg/m^2/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m^2/day). The doses of 0.02, 0.04, 0.08, and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51, and 318.7 times the minimum recommended dose of 110 mcg of Nasacort per day and 3.2, 6.4, 12.7, and 80 times the maximum recommended dose of 440 mcg of Nasacort per day based on a patient body weight of 70 kg. Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Nasacort Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in children below the age of 12. Oral corticoids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS: In controlled and uncontrolled studies, 1257 patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed Nasacort canister. These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days).

The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received Nasacort. Nasal irritation was reported by 2.8% of the patients receiving Nasacort. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received Nasacort and included: dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects.

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).

OVERDOSAGE: Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects if the nasal application of the 15 mg of triamcinolone acetonide was administered all at once.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Please see product circular for full prescribing information.

REFERENCES:

1. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc. **2.** Ziemniak JA: Pharmacokinetics of intranasal triamcinolone acetonide. *J Respir Dis* 1991;12 (3, Suppl):S41-S42. **3.** Feiss G, Morris R, Rom D, et al: A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function. *J Allergy Clin Immunol* 1992;89:1151-1156. **4.** Findlay S, Huber F, Garcia J, et al: Efficacy of once-a-day intranasal administration of triamcinolone acetonide in patients with seasonal allergic rhinitis. *Ann Allergy* 1992;68(3):228-232.

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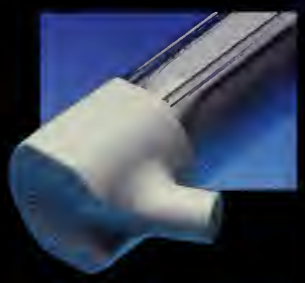
QD STAYING POWER

Positron emission tomography (PET) image of ^{11}C-triamcinolone acetonide following intranasal administration of Nasacort[1]



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Nasacort®

(triamcinolone acetonide) Nasal Inhaler

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Article

Attitudes of Washington State Physicians Toward Health Care Reform

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Attitudes of Washington State physicians about health care reform and about specific elements of managed competition and single-payer proposals were evaluated. Opinions about President Clinton's reform plan were also assessed. Washington physicians (n = 1,000) were surveyed from October to November 1993, and responses were collected through January 1994; responses were anonymous. The response rate was 80%. Practice characteristics of respondents did not differ from other physicians in the state. Of physicians responding, 80% favored substantial change in the current system, 43% favored managed competition, and 40% preferred a single-payer system. Of physicians responding, 64% thought President Clinton's proposal would not adequately address current problems. Reduced administrative burden, a central element of single-payer plans, was identified by 89% of respondents as likely to improve the current system. Other elements of reform plans enjoyed less support. More procedure-oriented specialists than primary care physicians favored leaving the current system unchanged (28% versus 8%, $P < .001$). While physicians favor health care reform, there is no consensus on any single plan. It seems unlikely that physicians will be able to speak with a single voice during the current debates on health care reform.

(Malter AD, Emerson LL, Krieger JW: Attitudes of Washington State physicians toward health care reform. West J Med 1994; 161:29-33)

Physicians' attitudes on proposed health care reforms are an important element of the current reform debate because of their central role in health care delivery. Physicians are in a unique position to provide feedback about the feasibility of proposed reforms and about their possible effects. Also, the ultimate success of any enacted reforms will depend upon the support of all those working within the new system, including physicians.

Physicians' attitudes about health care reform have not been well studied. Blendon and colleagues recently reported on the attitudes of Canadian, German, and United States physicians toward the current health care systems in their respective countries.[1] We were unable to locate any reports in peer-reviewed journals about physicians' preferences for those health care reform plans currently under consideration in the United States, however. Surveys and polls of physicians' attitudes are occasionally reported in nonpeer-reviewed literature, but the results can be difficult to interpret because methods are rarely described and the possible biases of sponsoring organizations are unclear.[2]

To help policy planners better understand the attitudes of physicians toward health care reform, we surveyed 1,000 Washington State physicians. The attitudes of Washington physicians are of particular interest because the state has already enacted managed competition reform similar to that being proposed nationally. Physicians were active during the legislative debates that compared the merits of managed competition and single-payer systems and have a reasonable understanding of the features of these competing reform options. Our survey concentrated on physicians' attitudes toward managed competition and single-payer systems because these two approaches to reform underlie the specific proposals that are receiving the most serious consideration nationally.

Methods

Our sample of 1,000 physicians was selected randomly from a list supplied by the Washington State Department of Health of the 11,054 physicians actively practicing in the state. The sample size was larger than that needed to estimate the attitudes of all state physicians and was chosen to allow analyses of subpopulations. Surveys were mailed from October to November 1993, soon after President Clinton delivered his health care reform package to Congress.

A two-page questionnaire was developed for this study. Selected survey items are shown in Tables 2 and 3, and the full instrument is available from the authors. The two-page survey was composed of 24 questions: 6 on the general attitudes about health care reform, 11 on specific elements of alternative reform packages, and 7 on demo-

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TABLE 1.—*Demographic and Practice Characteristics of Survey Respondents Compared With Those of All Washington Physicians*

Characteristic	*Respondents (n = 762)*	*All State Physicians (n = 11,054)*
Male sex, %	85	81*
Metropolitan practice (population >250,000), %	73	74
Years of practice, median	18	17
Specialty		
General practice or family practice, %	19	19
Adult medicine or medical sub specialties, %†	21	23
Pediatrics or pediatric subspecialties, %	7	7
General and specialty surgery, %	20	18
Obstetrics and gynecology, %	6	5
Radiology, anesthesiology, or pathology, %	13	13
Other, %	14	15
Reimbursement mechanism		
Fee-for-service, %	65	‡
Salaried, HMO, %	11	‡
Salaried, non-HMO, %	12	‡
Other, %	12	‡

HMO = health maintenance organization

*Sex of respondents and all state physicians differed significantly ($P > .01$); other characteristics of respondents and all state physicians did not differ.

†Includes neurology.

‡Not available.

graphic and practice characteristics. All items were developed specifically for this survey except a general question regarding the perceived need for reform of the health care system, which was developed by Blendon and colleagues and has previously been administered to a sample of physicians nationwide.[1] Its inclusion allowed a comparison of general attitudes of physicians in our sample with those of all US physicians. The survey was tested on practicing physicians who rated the questions as easily understood. The face validity of the final instrument was confirmed by health care reform experts. The internal consistency of the instrument was evaluated for selected survey items that were expected to be correlated. Cronbach's test showed reasonable internal consistency for these items ($\alpha = .53$ to $.70$).

The survey was mailed on University of Washington stationery, accompanied by a cover letter that described the study and noted that responses would be kept anonymous. The letter also noted the endorsement of three health care provider organizations with different stands on health care reform: the Washington State Medical Association (which generally supports the version of managed competition enacted by Washington State), Health Care for All (a statewide health provider organization promoting single-payer reforms), and WAMI (a popular educational system serving rural physicians, which has not taken a position on reform). Respondents were identified from name cards that were included in the mailing but separated from the surveys on receipt. Physicians not responding within three weeks were mailed a second copy of the survey. Responses were collected from November 1993 through January 1994.

Demographic and practice characteristics of respondents were compared with those characteristics of all state physicians using a two-sided z test.[3(pp230-231)] Characteristics for all active state physicians were based on information in the American Medical Association's master file and state data tapes.[4(p181)] The main analyses were descriptive, and 2×2 χ^2 analysis was used to determine whether any demographic or practice characteristics predicted physicians' attitudes on health care reform. Confidence intervals for proportions were computed assuming a normal distribution according to the method described by Altman.[3]

Results

Of the 1,000 mailed surveys, 46 were not deliverable. Of those delivered, 762 were completed and returned, for an overall response rate of 76% and an effective response rate of 80%. Of completed surveys, 69% were returned after the first mailing. The demographic and practice characteristics of the respondents are shown in Table 1. Most respondents worked in urban counties and received fee-for-service payment. Respondents were similar to all state physicians except for a slightly higher proportion of men.

Physicians' general attitudes about health care reform are shown in Table 2. When asked about preferred options for change, there were no significant differences in the proportions favoring the single-payer and managed com-

TABLE 2.—*General Attitudes of 762 Washington Physicians Toward Health Care Reform**

	Physicians Agreeing, %	*95% Confidence Interval, %*
Which of the following statements most closely expresses your view of the current American health care system?		
In general, the health care system works pretty well, and only minor changes are necessary to make it work better	20	17-23
There are some good things in our health care system, but fundamental changes are needed to make it work better	71	68-74
The health care system has so much wrong with it that we need to rebuild it completely	9	7-11
Which of the following changes in the American health care system would you favor most?		
No change	16	13-19
A system based on managed competition between several private insurance plans in which employers are required to offer employee health insurance	43	39-47
A single-payer system in which everyone receives coverage from a single, publicly accountable plan	40	36-44

*Data for 17 respondents were missing for the first question and data for 65 were missing for the second; percentages may not add up to 100% due to rounding error.

TABLE 3.—*Attitudes of 762 Washington Physicians Toward Specific Elements of Reform Proposals**

	Percentage Responding				
	None	*A Little*	*Some*	*A Lot*	*Undecided*
How much confidence do you have that each of the following approaches would improve the health care system?					
Caps for health insurance premiums	22	22	28	19	9
Requiring employers to provide insurance	15	24	36	23	3
Increased utilization review by insurers	46	31	18	4	2
Reduction of administrative paperwork	2	8	21	68	1
A uniform benefit package for all patients	16	17	28	35	4
A global health care budget	36	17	21	16	11
Increased use of practice parameters	9	28	37	18	7
Uniform fees for physicians	27	21	27	19	6
Malpractice reform	4	9	24	62	1

*Data for 6 to 25 respondents were missing for each question; percentages may not add up to 100% due to rounding.

petition approaches. When specifically asked whether the Clinton Plan would address the shortcomings of the current system, 33% responded that the plan has "some" chance of addressing the shortcomings of the current system, and 3% thought it had a "good" chance, but 61% thought the plan had little or no chance of addressing these shortcomings. A majority (72%) indicated that they understood the Clinton Plan "some" or "a lot."

When asked about the likelihood that specific elements of alternative reform plans would improve the health care system, physicians rated reduction of administrative paperwork and malpractice reform highly, but otherwise responses were divided (Table 3). Physicians' preferences for health care reform plans, stratified according to physician specialty, are shown in Table 4. More so-called procedure-oriented specialists (surgeons, obstetrician-gynecologists, radiologists, anesthesiologists, and pathologists) than primary care physicians (family practitioners, general internists, and general pediatricians) favored leaving the current system unchanged (28% versus 8%, $P < .001$). Regarding the type of change preferred, more primary care physicians favored a single-payer system than did procedural specialists (47% versus 27%, $P < .001$). Managed competition had equal support in both groups. Among those favoring some type of change, support for reform options varied according to practice specialty. Most pediatricians and psychiatrists favored a single-payer plan while surgeons favored managed competition. Other groups were equally divided.

The reimbursement mechanism also predicted preference for reform plans. Salaried physicians were approximately 1.5 times as likely to favor a single-payer system as were fee-for-service practitioners (50% versus 34%, $P < .001$). Fee-for-service physicians were three times as likely to favor no change (22% versus 7%, $P < .001$). Equal proportions of both groups favored managed competition (44%). Other demographic and practice characteristics were not significantly associated with attitudes toward reform.

Discussion

Our results show that although physicians generally favor health care reform, there is no consensus on any single reform proposal. Comparable percentages of physi-

TABLE 4.—*Physicians' Preferences for Health Care Reform According to Specialty (n = 686)**

	Preferred Reform Proposal			
Specialty	*Physicians, No.*	*None, %*	*Managed Competition, %*	*Single Payer, %*
Primary care	250	8	44	47
General and family practice	132	11	46	42
General internal medicine	82	5	48	48
General pediatrics	36	6	31	64†
Procedure-oriented specialties	264	28	46	27
Surgery‡	178	29	46	25†
Radiology, anesthesiology, and pathology	86	24	44	31
Other				
Medical and pediatric subspecialties	77	8	48	43
Psychiatry	48	11	25	65†
Emergency medicine	33	15	42	42
Other	14	21	29	50

*Data for the other 76 respondents were missing.
†Proportions favoring managed competition and single-payer systems differ significantly ($P < .05$).
‡Including general surgery, surgical subspecialties, and obstetrics and gynecology.

cians reported favoring managed competition and single-payer systems. These physicians had little confidence that President Clinton's managed competition proposal would improve the current system. The element of reform viewed as most likely to improve the current system by the greatest number of respondents was reduced administrative burden. Although both managed competition and single-payer plans offer this potential, the Congressional Budget Office and others have concluded that administrative burden and costs are much lower in a single-payer system.[5-7] Malpractice reform also enjoyed considerable support. Other components of managed competition and single-payer plans enjoyed substantially less support; opposition was strongest to increased utilization review.

We also found that physicians' attitudes on the need for reform vary according to specialty. Procedure-oriented specialists were more than three times as likely as primary care physicians to think that change in the current health care system is unnecessary. This may reflect the fact that procedural specialists may be less aware than primary care physicians of problems such as lack of access and insurance because they generally only see referred patients. Alternatively, it may have to do with the fact that on average these specialists enjoy greater remuneration under the current system.[8] Both approaches to reform advocate expanded roles for primary care physicians and a reduced use of specialty services.

Of physicians favoring change, psychiatrists, pediatricians, and salaried physicians tended to favor single-payer systems, whereas procedure-oriented specialists and those practicing fee-for-service medicine favored managed competition. This may reflect differences of opinion among the specialty groups about the best roles for government and private insurers in the financing of health care. It may also reflect differing views among the groups about access and the quality of care their patients would receive under the two reform plans. Procedural specialists may be concerned that single-payer reform will lead to more substantive changes in their current practice than will managed competition. This may not be justified because authorities have commented that a single-payer system may better preserve current practice patterns than managed competition.[9,10]

The effective response rate of 80% minimizes threats to external validity and indicates that the results can be generalized to all Washington State physicians.[11,12] Further evidence of external validity is the similarity of practice characteristics of respondents to those of all state physicians. The high response rate is likely a reflection of the topical nature of the issue. The initial mailing of the survey occurred a week after President Clinton delivered his health care package to Congress. In addition, the endorsements of three organizations with differing stands on health care reform may have increased the response rate by allaying any concerns that survey sponsors were biased.

A limitation of this study was our choice to focus the survey on managed competition and single-payer proposals. That seemed reasonable because these two approaches underlie the reform proposals that are currently receiving the most serious consideration nationally. In addition, the two reform alternatives that mandate universal coverage—a provision President Clinton has indicated is necessary for his support—are based on managed competition and single-payer systems. Another limitation is that data were incomplete for some survey items. Of respondents, 9% failed to specify preferred options for health care reform. It is unlikely that these physicians strongly favored either of the two reform plans listed. Rather, they most likely favored no change or an option not presented. Thus, although managed competition and single-payer reforms may enjoy slightly less support than shown, they are still likely to be equally favored. A final limitation is that physicians' attitudes may have changed since the survey was conducted. For example, although only 25% of surgeons we surveyed favored single-payer reforms, the governing board of the American College of Surgeons recently expressed support for this plan. It is not clear whether the attitudes of most surgeons are consistent with the position of their College or with those expressed by the Washington surgeons.[13]

Other studies of physicians' attitudes on health care reform were reviewed, but only one was located that compared attitudes on managed competition and single-payer systems. The study, commissioned in October 1993 by the American Medical Association (AMA), was a phone survey of 400 physicians selected from the AMA master file of all US physicians (H. Meyer, written communication, Report of the Board of Trustees, American Medical Association). Physicians were asked about how they and their patients would fare under Clinton's proposed managed competition plan and a single-payer plan, as well as the AMA's Health Access America plan. In this survey, 43% thought their patients would do "better" or "the same" under the Clinton plan, 46% under a single-payer plan, and 54% under the AMA's plan. Results must be considered cautiously, however, because it is not clear what the response rate was and whether respondents could have been biased toward the AMA's plan because it was sponsoring the survey. In a 1993 study comparing US, Canadian, and German physicians, Blendon and coworkers reported that 80% of physicians in the United States thought that the current system required substantial change, but attitudes about the type of change preferred were not elicited.[1] A 1989 survey of resident physicians in ten states found that 87% supported a private fee-for-service system, but 42% also indicated that they could support national health insurance as an alternative.[14] Attitudes about managed competition were not gathered in the study. Anecdotal reports have suggested that US physicians oppose a single-payer system, but at least one of these reports appears to be based on a biased sample.[15] In addition there is evidence to suggest that physicians have more cautious attitudes on health care reform than does the general public. Although 29% of the US population favors completely rebuilding the current health care system, both this study and Blendon's found this attitude was held by only 10% of physicians.[1,16]

The attitudes of Washington physicians about health care reform may be unusual. Washington physicians may be more informed than the average US physician regarding the merits of alternative reform plans because the state has already debated and adopted health care reform. They may also understand the implications of a managed competition system more fully than their out-of-state colleagues because this type of reform is currently being implemented statewide. Nonetheless, there is reason to think that the attitudes of Washington physicians on managed competition and single-payer plans may reflect attitudes evolving among all US physicians. First, in its nationwide survey, the AMA also found that similar proportions of physicians felt their patients would fare as well or better in the future under single-payer or managed competition plans (46% versus 43%, H. Meyer, written communication, Report of the Board of Trustees, American Medical Association).

Second, in their survey of US physicians, Blendon and colleagues reported that 80% of responders thought the current system required fundamental changes or greater.[1] This is the same percentage that we observed in Washington physicians answering an identical question. The similarity in attitudes about reform may indicate that comparable percentages of physicians nationwide will also favor managed competition and single-payer systems.

Conclusion

Because of physicians' central role in the health care delivery system, they are likely to have important insights about the feasibility of proposed reforms and their possible effects. Therefore, the physicians' attitudes observed in this study should be considered during the current debates about health care reform. We found that there is no consensus on any single reform proposal, although physicians have little confidence that managed care will improve the current system. The element viewed as likely to improve the current system by the greatest number of respondents was reduced administrative burden, a central element of single-payer reform. Elements viewed least favorably were those aimed at controlling costs and increasing external review of clinical practice. Physicians' attitudes on reform depend on specialty. This variation in physicians' views suggests that they will not be able to speak with a single voice on health care reform in the near future.

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Articles

Continuing Medical Education About AIDS—A Needs Assessment

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The incidence of the acquired immunodeficiency syndrome (AIDS) among Latinos and African Americans nationally and in Los Angeles has risen substantially. No data exist to indicate which physicians (or groups of physicians) provide care to these groups, however. To better plan AIDS educational programs, efforts were made to identify those physicians whose offices were located in areas with high proportions of nonwhites. Many physicians in these areas—30% of all office-based primary care physicians in Los Angeles—were found to be graduates of international medical schools. A survey of a stratified random sample of international medical graduates revealed that compared with a random sample of United States medical graduates, they had a greater proportion of nonwhite patients, often of an ethnicity similar to theirs; practiced in areas with a greater proportion of Asians and lower family incomes; had fewer patients infected with the immunodeficiency virus (HIV) in their practices; and were more avoidant of such patients.

As the incidence of HIV infection increases among minority groups, means need to be developed to ensure their access to counseling and screening, as well as treatment with the latest available agents. Options include imaginative and engaging approaches to continuing medical education for all physicians and the creation of separate public sector infrastructures to meet the HIV-related needs of these communities.

(Lewis CE, Carlisle D: Continuing medical education about AIDS—A needs assessment. West J Med 1994; 161:34-38)

In 1987 the Health Resources and Services Administration, through its Bureau of Health Professions, Division of Medicine, responded to section 778A of title VII of the Public Health Service Act by creating a network of AIDS [acquired immunodeficiency syndrome] Education and Training Centers spanning the United States. These centers were mandated to provide education to health care professionals to deal with the emerging problem of human immunodeficiency virus (HIV) infection and AIDS. One of these centers, that for southern California, includes an area that contains between 8% and 9% of the more than 300,000 cases of AIDS reported as of late 1993. The institutions composing this AIDS Education and Training Center have offered programs to students of the professions and practitioners of medicine, dentistry, and nursing that include seminars, workshops, and clinical "hands-on" experiences. A series of needs assessments has also been done. We summarize the latest of these.

Under ideal circumstances, educational needs assessments involve the testing of practitioners or trainees to determine deficits in knowledge, skills, and orientations that affect their clinical competencies. This usually involves administering standardized tests, but has expanded to include clinical problem-solving examinations and even the use of standardized patients.[1,2] Controlled testing circumstances, however, are not available to those who design continuing medical education for physicians in practice. Few practitioners are willing to invest the time (or place themselves at any potential risk) to take such "tests." As a result, surveys have been used as a proxy. But surveys at best can provide descriptions of practitioners' experiences, their perceived competencies, and the extent to which (they say) they perform specific functions that are deemed essential to provide care to certain patients. Of course, socially desirable responses may color their responses to these surveys. In the absence of behavioral measures of competency of individual physicians, such surveys can be used to define relative priorities in targeting specific groups of physicians in a community for more extensive efforts designed to promote their voluntary participation in educational programs.

Since 1984 we have conducted surveys of random samples of primary care physicians in Los Angeles County at two-year intervals to determine the physicians' AIDS-related experiences, beliefs, and practices.[3,4] The

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CI = confidence interval
HIV = human immunodeficiency virus
UCLA = University of California, Los Angeles

1990 survey suggested that a lesser proportion of international medical graduates was providing primary care in Los Angeles for HIV-infected patients than the percentage of primary care physicians from United States medical schools seeing these patients.[5] The data from that survey did not answer the question, Why? Is this a function of their seeing fewer patients at risk or a failure to recognize patients at risk, or is it related to an avoidance of caring for HIV-infected patients? The purpose of this report is to describe a sequential effort designed to answer this question (why?) and to define more precisely those physicians who should be targeted for the educational efforts of the AIDS Training and Education Center of Southern California.

Approach

To plan AIDS educational efforts for physicians in practice, several questions must be answered:

- Where is the AIDS epidemic going; that is, which subgroups of the population have the greatest incidence of infection?
- Where and from whom do these high-risk groups seek care?
- How well qualified in dealing with HIV infections are those physicians from whom they seek care?

Where Is the Epidemic Going?

Data on the distribution of AIDS cases reported in 1987 in Los Angeles by ethnic subgroups revealed that 60% of the reported cases were among whites, 18% were African Americans, 19% were Latinos, and 1% were Asians.[6] In 1992 in Los Angeles, the racial or ethnic distribution of newly reported cases of AIDS had changed. Only 49% occurred in whites, and 21% occurred in African Americans (an increase of 36%). The largest increase in cases was among Latinos. In 1992 they represented 30% of all new cases, compared with 19% in 1988, or an increase of more than 60%. Asians accounted for 2% of AIDS cases in 1992. Thus, in Los Angeles and elsewhere in the United States, the greatest increases in the incidence of new cases of HIV infection or AIDS were among Latinos and African Americans.[7]

Where Do African Americans and Latinos Seek Care?

No recent data are available from Los Angeles County that explain where African Americans and Latinos seek care. Several surveys involving national samples, participants in the Community Hospital Program and the Municipal Health Services Program, as well as households in Arizona and New York City, do provide such data. All were conducted by a nationally known survey firm (Louis Harris).[8 (p241)] Funding for the surveys was provided by the Robert Wood Johnson Foundation or the Health Care Financing Administration. All used survey instruments developed by the Center for Health Administration Studies at the University of Chicago.

These surveys involved 8,938 Latinos and African Americans chosen at random from the sites or programs previously noted. They suggest that most respondents from both minority groups—with or without insurance—reported a private physician as their regular source of care. Specifically, 71% of Latinos and 59% of African Americans surveyed across the United States cited "private physicians' offices" as their usual site of care. In these several studies, from 12% to 20% of Latinos and African Americans said they had no regular source of care. Rather than hospitals, clinics, emergency departments, or other facilities, however, private physicians' offices were the predominant source of care for these groups in all of these studies. This may surprise those who hold a vivid image of the emergency and clinical facilities in the public sector exclusively filled with members of these groups waiting to be served.

Thus, it seems appropriate, based on these findings (collected from 1982 to 1985), to assume that in Los Angeles, primary care physicians provide a majority or a substantial amount of the ambulatory care received by these high-risk populations. But which physicians? Almost no data exist on the patient care mix (race or ethnicity) of patients seen by particular subgroups of physicians. One exception is a 1982 study of graduates of Howard University Medical School, Washington, DC. The 252 African-American physicians responding reported that an average of 67% of their patients were African American.[9]

Patients with fewer resources, including transportation, might be assumed to visit primary care physicians whose offices are located in their community; thus, the ethnic mix of the community might mirror a physician's practice. We also tested a second and confounding hypothesis, that persons tend to seek physicians of a similar ethnic identity (near them).

Physicians and Methods

To confirm and update the findings of the 1990 survey, another survey was conducted in mid-1992 involving a random sample of all office-based primary care physicians—family medicine, general practice, and general internal medicine—in Los Angeles County (n = 4,420). Although international medical graduates represent 30% of all primary care physicians in the county, this group was oversampled to ensure an adequate number for statistical comparisons.

The American Medical Association's master file was used to identify United States and international medical graduates in office-based primary care practice in Los Angeles County. Identifying African-American and Latino US medical graduates in this analysis was not possible because data on race or ethnicity do not exist in the master file and a considerable proportion of minority physicians are no longer graduates of "traditional black medical colleges."

TABLE 1.—*Average Racial and Ethnic Compositions of Office Patients and Areas Where Offices Are Located*

International Medical School Graduate	No. Responded/ No. Surveyed	Patients, %					Population in Zip Code Area, %			
		Latino	African American	White	Filipino	Asian	Latino	African American	White	Asian
Philippines	32/38	24	7	30	22	17	38	4	35	23
Latin America	14/18	65	3	29	2	1	51	4	35	10
Guadalajara*	30/36	24	5	63	3	5	24	3	58	15
Guadalajara†	7/8	86	2	10	1	1	60	2	22	16
Totals	83/100	36	5	40	10	9	37	3	42	18

*Candidates with non-Latino names.
†Candidates with Latino names.

The survey was conducted by the Institute for Social Science Research at the University of California, Los Angeles (UCLA). Interviews took from 20 to 30 minutes to complete. As many as six callbacks were made before a person was considered a nonrespondent. A total of 202 physicians were interviewed: 102 US medical graduates and 100 international medical graduates. The 100 international medical graduates in office-based primary care practice who had responded to the survey were sent an additional inquiry. These included graduates of Philippine Islands medical schools (n = 38), Latin-American medical schools (n = 18), and a subset from Guadalajara, Mexico (n = 44). These physicians were sent letters asking them to complete and return an enclosed card describing the patient mix in their practice: the percentage of their patients who were white, African American, Latino, Filipino, and Asian. A small token of appreciation, a UCLA lapel pin, was enclosed. The Guadalajara group had been oversampled in the original survey because they included about 20% of physicians with Latino surnames (Gonzales, Chavez, Valdez, and the like), whereas most had non-Latino surnames (Monroe, Sheldon, Williamson). Increasing the proportion surveyed provided an opportunity to contrast these two subgroups of international medical school graduates.

We analyzed the associations among the office locations of all US and international medical graduates providing office-based primary care in Los Angeles County, not just those in the sample. The population-area descriptors used in these analyses were the relative percentages of four population groups—white, African American, Latino, and Asian—in the zip code where a physician's office was located. The median household income, mean age of the population, and the total population of each zip code were also used in the analyses. Bivariate associations were examined, and, finally, multiple logistic regression analysis was done to determine significant predictors of physicians' locations.

In this analysis, only zip codes with greater than 5,000 residents were included, and nonresidential zip codes were excluded. A total of 253 zip codes in Los Angeles were represented in the analysis. International medical graduate offices were located in 93 zip code areas, or 36.8%.

Results

After controlling for age, income, and population size, the significant predictors for the location of primary care international medical graduates were lower family income (odds ratio = 3.0; confidence interval [CI] = 1.43 to

TABLE 2.—*Human Immunodeficiency Virus (HIV)-Related Characteristics and Experiences of Physicians*

Characteristic	US Medical School Graduate (n=102)	International Medical School Graduate (n=100)	Total (n=202)
Completed telephone interview, %	71.1	77.3	74.1
Internal medicine practice, %	48.1	38.2	45.0
Average No. of patients/wk	80.0	93.0*	84.0
Solo practice, %	49.0	69.9*	55.4
Accept Medi-Cal, %†	35.6	55.3*	41.6
Evaluated patient for HIV, %	69.2	55.3	65.0
Have HIV-positive patient(s), %	42.3	20.4‡	35.6
HIV-positive patients came with diagnosis, %	68.2	61.9	67.1
Have patient(s) with AIDS, %	29.8	11.7§	23.6
Take routine sexual histories on new patients, %	67.3	47.6*	61.3
Ask about No. of partners, %‖	47.4	73.2	61.3
Ask about sex of partners, %‖	64.1	71.4	65.9
Of those seeing HIV-infected patients			
Have prescribed zidovudine, %	40.1	13.6‡	27.1
Prescribed PCP prophylaxis, %	39.6	12.3‡	27.1

AIDS = acquired immunodeficiency syndrome, PCP = *Pneumocystis corinii* pneumonia

*$P<.05$. †California's Medicaid. ‡$P<.001$. §$P<.01$. ‖This question applied to those who report taking a sexual history.

TABLE 3.—*Factors Associated With Absence of Human Immunodeficiency Virus (HIV)-Positive Patients in Practice*

Factor	US Medical School Graduates, %	International Medical School Graduates, %	Total, %
Why do you have no HIV-positive patients?*			
Not encountered	39.0	42.0	40.1
Referred elsewhere	39.0	49.4	42.9
If HIV-positive patient presented			
Accept	43.2	19.0	35.1
Refer	58.8	81.0†	64.9
Why do you not accept HIV-positive patients?*			
Too complex	89.2	93.7	91.2
Feel inadequately prepared to care for HIV-positive patients	29.8	57.8‡	38.3
Satisfied with level of preparedness	85.3	86.1	85.5

*Percentage of those who did not have an HIV-positive patient in their practice. †P<.01. ‡P<.001.

6.15) and a higher percentage of the Asian population in the area (odds ratio = 4.1; CI = 2.24 to 7.62). Bivariate analysis showed a higher number of US medical graduates in areas with smaller populations, higher median incomes, older populations (median age), a higher proportion of whites, and a lower proportion of Latinos and African Americans (all significant, $P < .01$). Multivariate analyses of the predictors of location of US medical graduates in primary care practice revealed that after adjusting for all variables, the single significant predictor was a low percentage of Latinos in the area (odds ratio = 0.42; CI = 0.18 to 0.95). The predictors of the total number of primary care physicians were a higher proportion of whites (odds ratio = 3.08; CI = 1.38 to 6.91) and a lower proportion of Latinos (odds ratio = 0.35; CI = 0.16 to 0.79).

The results of the physician-patient mix survey and the geographic analyses are shown in Table 1.

Graduates of Philippine medical schools had a greater proportion of Asian patients, especially Filipinos, in their practices, and their offices were located in zip code areas with high proportions of Asians. The same parallel was seen for graduates of Latin-American medical schools. Graduates of Guadalajara with Latino names had the highest (average) proportion of Latino patients, which was in pronounced contrast to their non-Latino-surnamed fellow alumni. The proportion of African Americans in an area was not a predictor of the location of either international or US medical graduates or total number of primary care physicians. All had rather low proportions of African Americans in their practice—lower than the overall population in Los Angeles County (12%).

Table 2 provides a summary of the results of the telephone survey, weighted to adjust for the sampling proportions.

The overall completion rate was 74%. As indicated, international medical graduates saw a significantly greater number of patients per week. More were in solo practice, and more accepted Medi-Cal (California's Medicaid) patients into their practice.

Although there was no difference in the proportion of those who said they had evaluated a patient for HIV infection, the proportion of US medical graduates having an HIV-positive patient under continuing care was more than twice that of international medical graduates (42.3% versus 20.4%). The same was true in terms of the proportion who were caring for AIDS patients in their practice (29.8% versus 11.7%).

Although a significantly lower proportion of international medical graduates took routine sexual histories on new patients, those who did more frequently asked about the number of partners and the sex of the partners as part of that history than did US medical graduates.

Table 3 summarizes factors associated with the absence of HIV-infected patients in practices. The proportion of both groups who had not seen an HIV-infected patient and who referred such patients elsewhere was similar. The proportion of physicians in this sample who refused to care for HIV-infected patients (35.6%) is almost identical to that reported in 1990 (36.0%).[10] When asked if they would accept an HIV-infected patient who presented to their practice, a significantly greater proportion of international medical graduates (81% versus 19%) said they would choose *not* to accept that patient into their practice.

In the interview, physicians were offered various reasons why persons might choose not to accept such patients. Of both groups, 5% to 15% cited concerns by their staff and personal concern over infection. More than 90% of both groups, however, felt that these patients were "too complex (for them) to manage." "These" patients were carefully described as HIV-infected patients without symptoms.

Physicians were asked if they felt adequately prepared to care for HIV-infected patients. Almost twice as many international medical graduates answered no to this question as did US medical graduates (57.8% versus 38.3%). Later in the interview, they were asked how satisfied they were with their level of preparedness to provide care to HIV-infected patients. As shown in Table 3, more than 85% of both groups felt very or somewhat satisfied. Thus, a significant proportion of physicians who said they were satisfied with their level of preparation to provide care to HIV-infected patients also indicated they were inadequately prepared to do so (17.3% of US medical gradu-

ates and almost half, or 48%, of international medical graduates).

As in the 1990 survey, a majority of both groups of physicians (with no difference between the two groups) expressed interest in further continuing medical education related to HIV disease.

Discussion

A recently published study of primary care practitioners in 44 practices in the Ambulatory Sentinel Practice Network documented the importance of primary care providers in responding to the AIDS epidemic.[11] Of the 9,747 persons tested who came to participating physicians for any reason, 2.3 per 1,000 were found to have antibodies to HIV. In almost half of these cases (1.0 per 1,000), their physicians did not know that they were infected.

This study involved a random sample of physicians in the office-based private practice of primary care in Los Angeles County, and clearly the results cannot be generalized to other communities. Through a series of steps, we have defined, from an epidemiologic perspective for the purposes of continuing education about AIDS, a high-priority group of physicians in private practice who serve Latino patients in this area. The data presented here deal only with the care of those with HIV infection and cannot be interpreted as a general comment on the overall quality of primary care provided by these international medical graduates. The quality of care provided by US and international medical graduates has been compared in a limited number of inquiries. Although those who graduated from medical schools outside the United States tend to score lower on boards in internal medicine than US medical graduates,[12] a study of the quality of care provided, assessed through medical records reviews, suggested that the difference is attributable more to the hospital where physicians practice than to the site of their medical education.[13]

International medical graduates may feel less prepared and less willing to accept HIV-infected patients for several reasons. They may not have had formal training in sexual history taking as undergraduates or in their residency programs (unless they have recently immigrated to the United States). Some are caring for subgroups of patients who are more concerned or anxious about discussing human sexuality than are white middle-class patients. Also, HIV-infected patients *do* require additional time, and, as reflected in Table 2, international medical graduates tend to see more patients per week than US medical graduates. They also tend to see patients whose insurance (if any) provides less remuneration, thus suggesting a reason for a higher volume or patient-load. Whereas these international medical graduate subgroups have expressed, through the surveys, an interest in further education, to date these offerings and their associated marketing efforts have failed to attract these physicians in substantial numbers.

The actual reasons that practitioners choose not to accept HIV-infected patients may be complex and may include religious and deep-seated cultural values. The only acceptable ethical reason a physician may give for not accepting a new patient for continuing care, however, is that the physician is not prepared or lacks the competency to render that care. It is unrealistic to ask physicians "why" they are not caring for these patients and expect them to respond with answers that reveal any personal biases (of which they may not be fully aware).

Given the results, we are left with the following options:

- Try to "educate" physicians about their responsibilities to the public (a somewhat hopeless venture);
- Recognize the lack of availability of services to certain subgroups of the population and attempt to create alternative systems to provide these services; or
- Some other alternative.

In Los Angeles, international medical graduates represent an important possible line of defense against the further spread of HIV infection in the minority community. Rather than blaming them for our collective problems in dealing with the HIV epidemic, we should also recognize that primary care US medical graduates who will not accept HIV-infected patients into their practices represent, in terms of numbers, a larger problem.[10] Options for dealing with "refusal to care" are limited. As is often the case in medicine, the diagnosis is relatively easy—the treatment is far more difficult.

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Articles

Medical Practice Guidelines

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Prescriptive standards of clinical conduct—practice guidelines—have proliferated throughout medicine over the past decade. Practicing physicians are confronted with a plethora of guidelines developed for different purposes by a diverse body of public and private organizations. We review factors contributing to the growth of guidelines, their desirable features, and consequences, legal and otherwise, of implementing guidelines. Few studies have examined whether, and under what conditions, guidelines are effective in changing physicians' practices and patients' health. Nonetheless, expectations for guidelines remain high because they are one of the only instruments of health care reform that promises to improve the quality of care while reducing overall health care costs. Efforts to develop guidelines are likely to continue unabated for the foreseeable future. Additional research comparing different methods of developing and disseminating guidelines is needed.

(Walker RD, Howard MO, Lambert MD, Suchinsky R: Medical practice guidelines. West J Med 1994; 161:39-44)

Practice guidelines have been used for half a century to facilitate effective decision-making by physicians.[1] The number of organizations developing guidelines has increased substantially in recent years. In 1990, there were 26 physician organizations responsible for creating more than 700 guidelines.[2] By 1992, these figures had risen to 45 and 1,500, respectively.[3] Many observers regard the proliferation of guidelines as part of "a significant cultural shift, a move away from unexamined reliance on professional judgment toward more structured support for, and accountability of, such judgment."[4(p2857)] Contemporary debate is focused on the role guidelines can and should play in health care reform.

Definitions of practice guidelines are proffered by a number of different organizations.[5-7] The Institute of Medicine describes guidelines as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.[8(p38)] Guidelines developed by the American Academy of Ophthalmology are referred to as "preferred practice patterns . . . because no two patients' needs are ever identical [and] 'cook book' medicine cannot ensure quality."[9(p67)] The American Medical Association refers to "practice parameters," emphasizing the view that guidelines must be flexible and allow for individualized treatment planning.[2] Perhaps the most straightforward definition is that developed by Shapiro and co-workers, who define guidelines as "statements of approaches to care for particular clinical situations."[10(p233)]

Although guidelines can take many forms, most definitions emphasize their common aim of improving physician decision-making by detailing appropriate indications for specific medical interventions. Implicit in most definitions is the notion that physicians should be allowed flexibility in responding to the particular circumstances of each patient. Eddy distinguishes between practice standards, which must be followed in nearly all cases, and practice guidelines, which permit greater flexibility.[11] According to Eddy, practice guidelines can be formulated when some important health results of an intervention are known, whereas practice standards require greater knowledge of the health and economic consequences of an intervention. To date, few practice standards have been developed and most guidelines do not incorporate cost considerations.

Developing Guidelines

The federal government is increasingly involved in developing guidelines. The principal mandate of the Forum for Quality and Effectiveness in Health Care, the office within the Agency for Health Care Policy and Research responsible for developing guidelines, is to develop, review, and update clinically relevant guidelines that may be used by physicians, educators, and health care practitioners to assist in determining how diseases, disorders, and other health conditions can most effectively and appropriately be prevented, diagnosed, treated, and managed clinically.[12(p6)]

Medical specialty societies have taken a leading role in developing guidelines. The Council of Medical Spe-

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cialty Societies and the American College of Physicians are strong proponents.[13] Other groups directly involved in developing guidelines include hospitals and health maintenance organizations, insurance, managed care, and utilization review companies, insurance carriers, voluntary organizations such as the American Cancer Society, and research centers, such as the Rand Corporation, the Academic Medical Center Consortium, and the Institute of Medicine.[1,14,15]

A number of other organizations support practice guidelines development. The Joint Commission on the Accreditation of Health Care Organizations asked medical specialty societies to make guidelines development a priority,[16] as have groups representing employer perspectives on health care issues.[17] Some states have promoted the development of statutorily imposed guidelines as a means of implementing malpractice reform.[18]

Guidelines are one of the few tools that can be used to control the volume and intensity of services offered to patients without sacrificing quality.[10] Thus, it is likely that federal involvement in guidelines development through agencies of the US Public Health Service such as the Food and Drug Administration, National Institutes of Health, Centers for Disease Control and Prevention, the Health Care Financing Administration, US Preventive Services Task Force, and the Congressional Office of Technology Assessment, will continue apace.

States have not been as active as the federal government in developing guidelines. The number of guidelines developed at the state level may increase in coming years, however, to the degree that health care reform occurs at the state rather than the federal level. Efforts to link practice guidelines and protection from malpractice liability in Maine are described later in the article.

Guidelines developed by private organizations, including those created by professional medical societies, are likely to increase in number. A recent General Accounting Office survey found that the two most common reasons for developing guidelines reported by 27 medical societies were improving quality of care and defending against external pressures such as malpractice litigation or conflicting guidelines for care established by other organizations.[19]

Factors Contributing to the Growth of Guidelines

Medical guidelines have proliferated over the past decade. Before 1980, eight medical societies had developed guidelines. Currently, more than 50 physician organizations are developing guidelines.[7] Medical specialty societies published more guidelines between 1990 and 1992 (800+) than they had before 1990.[3]

Investigations reporting high levels of inappropriate medical care are an important impetus to the development of guidelines. Nearly every study that has looked for the overuse of medical services has found it.[20] Many medical procedures are done at widely varying rates in different geographic areas.[21-23] Practice variation is assumed to imply an overuse of medical procedures in some geographic regions. The overuse of medical procedures, in turn, is attributed to physicians' uncertainty regarding appropriate indications for particular procedures. Contemporary observers maintain that physicians' uncertainty has increased because medical information is accruing at an unprecedented rate.[20] The rapid development of medical technologies and the fact that technologies are less concentrated also contribute to practice variation. Current practice trends are such that many patients are treated by physicians who are relatively inexperienced in applying certain treatment procedures. For example, the modal number of carotid endarterectomies done by surgeons attempting the procedure is one per year.[20]

Advocates of practice guidelines contend that they decrease physician uncertainty and reduce rates of inappropriate care by codifying knowledge in particular practice areas. They provide physicians with information in a form that is easy to use. A recent survey found that physicians wanted medical information in a form that is concise and directive.[24] Leape noted that "there is poor dissemination of clinically relevant information in a form that is useful to the practicing physician."[25(p43)]

Desirable Features of Guidelines

Although there was general agreement on the desirability of practice guidelines in 1990, Berman and Kaegi observed that greater attention to the processes by which guidelines were developed and disseminated was needed.[16] By 1992 Kaegi argued that the important questions had changed from who should develop practice guidelines and how should they be developed to what are the effects of practice guidelines on practitioner behaviors and patient outcomes and do practice guidelines increase treatment cost-effectiveness.[26]

Desirable characteristics of guidelines and reliable methodologies for implementing them have been identified. Most observers agree that guidelines should be widely disseminated,[3] based on a methodology open to public scrutiny,[27] revised regularly and in response to relevant scientific advances,[28] and derived from scientific evidence of the highest quality.[12] Leape suggests that guidelines should be comprehensive, including all indications for a procedure; specific, clearly describing conditions under which a treatment is recommended; inclusive, incorporating all factors that should be considered before recommending a procedure; and manageable, easy to understand and practice.[25] The Institute of Medicine suggests that guidelines should have validity—they should lead to the health and cost outcomes projected for them—clarity, clinical flexibility and applicability, and reliability and should be developed by a multidisciplinary process that includes participation by representatives of key affected groups.[8,19]

Contemporary protocols for developing guidelines have many common features:

- Reviews of extant research findings are conducted, often with the aid of the National Library of Medicine.
- Studies are selected according to predetermined cri-

teria and findings are summarized using techniques such as meta-analysis.

- Panels of experts are convened and guidelines are revised according to feedback received.
- Consensus is achieved in some areas and areas where disagreement or uncertainty remains and more research is needed are noted.

Although basic agreement has been achieved regarding the qualities practice guidelines should possess, relatively few investigations have assessed their effectiveness.

Do Guidelines Work?

Efforts to develop guidelines at the national level are frequently unsuccessful in changing physicians' practices, often because of the failure to adequately disseminate guidelines to target groups of practitioners.

A study done in Italy assessed whether a national education program based on a dissemination of practice guidelines for breast, colorectal, and ovarian cancer would affect physicians' knowledge, acceptance, and implementation of guidelines.[29] Guidelines were disseminated through booklets distributed to all general hospitals and at national scientific meetings. Physician concurrence with guidelines recommendations was unsatisfactory, and compliance with practice guidelines was highly variable. Evaluations of the National Institutes of Health Consensus Development Program reach similarly discouraging conclusions.[30] Medical care was examined before and after practice guidelines were introduced that addressed the surgical management of primary breast cancer, using steroid receptors in breast cancer treatment, cesarean childbirth, and coronary artery bypass surgical procedures. Guidelines were widely published in the lay and professional presses. Although moderate success was achieved in disseminating guidelines to appropriate target audiences, conference recommendations largely failed to change physicians' practices. The authors noted that it is notoriously difficult to change physicians' behaviors merely by providing information. They suggested that engaging the "active participation of the target audience in defining and disseminating the message" might be an effective diffusion strategy.[30(p822)]

The effects of distributing to obstetricians in Canada a consensus statement designed to reduce the incidence of cesarean sections among women with a previous cesarean section were assessed.[31] Questionnaires administered before and two years after the dissemination of guidelines indicated that obstetricians' knowledge of the content of the guidelines was poor and that their practices had changed little.

Guidelines developed by national organizations can affect the behavior of physicians if there are incentives encouraging their use. Guidelines adopted in 1984 by the American College of Cardiology detailing appropriate indications for pacemaker implantation were included in Medicare coverage policy and were widely accepted by physicians. These guidelines resulted in the more appropriate use of cardiac pacemakers and in notable reductions in the use of pacemakers in Medicare patients.[2] Anesthesiologists agreeing to adopt intraoperative monitoring guidelines developed by the American Society of Anesthesiologists in 1986 were offered a 20% premium reduction for liability insurance in 1987 by the Massachusetts Medical Malpractice Joint Underwriters Association. Before this agreement, anesthesiologists in Massachusetts averaged a total of six hypoxic events annually. Between 1987 and 1990, the insurance carrier registered no lawsuits related to hypoxia injury among physicians who followed the guidelines.[32]

Practice guidelines developed locally, or adapted to local conditions, are generally more effective than national guidelines disseminated to localities without consideration of their specific circumstances. Durand-Zaleski examined whether guidelines for treating hypovolemia could be successfully implemented in a 1,000-bed hospital.[15] Guidelines were aimed at reducing the use of albumin in favor of less costly treatments and were distributed to all physicians at the hospital, with meetings conducted for physicians from departments primarily concerned with treating hypovolemia. Monthly reports of the amount of albumin prescribed and its cost were provided to each physician. Implementing these guidelines was associated with a 40% reduction in albumin use in the following year. Implementing guidelines successfully was attributed to the intensity of dissemination, which included publishing guidelines in medical journals, direct mailings of guidelines to physicians, meetings, and the use of local physician opinion leaders.

The effects of status asthmaticus treatment guidelines on pediatric outcomes and pediatricians' behaviors within a large health maintenance organization were examined.[33] The recommendations of a national panel of experts served as the basis for the draft guidelines. Key personnel from several disciplines reviewed the guidelines and assisted in revising them. Guidelines development activities exerted positive effects: "The consensus process raised important issues and alerted the clinical staff to alternative practices as well as the latest recommendations in the management of acute asthma."[33(p472)] Comparisons between patients treated before and after guidelines were implemented found better results in patients treated under the new guidelines and important changes in pediatricians' behaviors. The authors of the report argue that local participation in guidelines development may move care closer to standards set by national panels of experts.

Guidelines for patients admitted to intensive care units were developed in 1990.[34] Draft guidelines were mailed to directors of intensive and coronary care units throughout Massachusetts, a meeting with these directors was convened to refine the guidelines, and statewide consensus on practice guidelines was achieved. For six months, a staff cardiologist reviewed the use of all intensive care unit beds daily to assess patients' need for continued intensive care unit care. This resulted in considerable reductions in the mean length of hospital stay and mean intensive care unit length of stay, relative to the baseline condition. Mortality and readmission rates were also reduced.

TABLE 1.—*Potential Effects of Practice Guidelines*

Positive Effects	*Negative Effects*
Help patients make informed health care decisions	May lead to "cookbook medicine"
Help physicians use appropriate health care technologies and reduce inappropriate care	May stifle innovative medical practice and the application of new technologies, particularly if guidelines are made the standard of care
Assist physicians in making cost-effective health care decisions	May increase medical costs by identifying interventions that are underused
Assist third-party payers in utilization review, performance rating, and reimbursement decisions	Cost reductions may not be substantial and may not outweigh costs of developing and updating guidelines
Serve as the basis for developing clinical indicators used to assess organizational competence and identify aberrant practitioners	May reduce research activity in areas where guidelines are developed
Could be used by physicians and organizations to improve practice	May contribute to disinterest in medicine as a career, quality of physicians may decline
May lower malpractice litigation costs by improving quality of care and serving as an "affirmative defense" in malpractice litigation	May provide inculpatory evidence in malpractice cases or increase malpractice litigation and costs or both
Medical textbooks and other educational materials could be organized around guidelines	

Several preliminary conclusions can be drawn from studies evaluating the effectiveness of guidelines in changing the behaviors of clinicians. Merely disseminating guidelines is not effective. Instead, incentives, such as reduced malpractice insurance premiums, should be offered to physicians to encourage them to use guidelines. Physicians or their representatives actively participating in the development process and local adaptation of national guidelines are potentially fruitful approaches. Using physician opinion leaders and physician profiling has proved effective in some studies.[34,35] In general, the more intense and diverse the dissemination and the more physician involvement, the more likely it is that physicians will be aware of guidelines and apply them in practice. Are some methods of developing guidelines particularly effective in shaping practitioners' behaviors? A recent Institute of Medicine report notes that, "As the guidelines development process evolves, more attention is being paid to who takes part in the process, when and how they participate, and what such participation should achieve."[19(p170)] Different methods of creating guidelines panels, selecting panel members, and identifying reviewers of draft guidelines should be compared. A particularly important issue is determining how patient preferences should be incorporated into developing guidelines. Research is needed on the following:

- What are the best techniques for eliciting patient preferences?
- What information and other conditions are required for informed and rational statements of preference?
- What are the technical and policy issues in quantifying individual preferences (utilities) and aggregating preferences for purposes of making judgments about what care is appropriate?[19(p181)]

Possible Consequences of Practice Guidelines

Some analysts contend that guidelines deleteriously affect the practice of medicine. Appelbaum questions whether guidelines codify knowledge in a way that stifles innovative medical practice.[36] Others argue that continuing investigation in a practice domain is undermined by the perception of agreement among expert panelists developing guidelines in that area.[30] "Cookbook medicine" may contribute to a disinterest in medicine as a career and the quality of new physicians may decline as the practice of medicine becomes increasingly perfunctory.

Legal implications of guidelines are the focus of several recent reports.[37,38] Bulger considers the possible liability of developers and users of guidelines, the respective roles of federal and state governments in institutionalizing guidelines, and the effect of guidelines on medical malpractice and decision-making, emerging issues of importance.[39] Many physicians are concerned that guidelines can provide inculpatory evidence that will be used against them in court as well as evidence that is exculpatory.[40]

The Maine Medical Liability demonstration project was established by the state legislature in an attempt to reduce the practice of defensive medicine by allowing physicians to use adherence to guidelines as a defense in malpractice cases. Special advisory committees from four medical specialties adapted national guidelines for local use. Guidelines were subsequently placed into law. Physicians agreeing to follow the guidelines—more than 50% in each specialty—are allowed to use adherence to the guidelines as an "affirmative defense" in malpractice litigation. The affirmative defense is intended to be raised early in the litigation process as it forestalls, if successful, lengthy hearings based on the merits of the case. Adherence to established guidelines can be raised by the physician-defendant in tort liability cases but cannot be used by the plaintiff. Data on the number of malpractice claims filed are not yet sufficient to evaluate whether the Maine project reduces malpractice litigation. Recent indications are that Vermont, Florida, and Minnesota may be developing similar programs.

Medical review organizations, and the physicians employed by them, may be vulnerable to malpractice suits if their actions are not in the best interests of patients. The Institute of Medicine recently cautioned that "prudence dictates that those applying them [practice guidelines] in medical review programs should expect to be held legally

accountable for their actions and should manage their affairs accordingly."[19(p118)]

One recent case involved a patient discharged from hospital on the basis of a recommendation derived from a clinical algorithm developed by the California Medicaid program (Medi-Cal), despite a physician's request for a few days of additional treatment. The patient, in whom complications later developed, sued Medi-Cal for negligence for requiring her physician to discharge her against his better judgment. The court observed that Medi-Cal and others who develop guidelines could be held liable for negligence resulting from the application of guidelines under some conditions and that physicians following review guidelines were liable to the extent that they did not exercise good medical judgment.[38]

Another important issue is whether guidelines should be used as the standard of care or simply as evidence of the standard of care. The American Medical Association and the Institute of Medicine support the use of guidelines as evidence of the standard of care, in preference to their use as mandatory standards, in malpractice cases.[19,41] Additional concerns are that mandatory guidelines could diminish the innovative practice of medicine and the application of new medical technologies. Table 1 outlines the possible positive and negative effects of practice guidelines.

Discussion

Expectations for guidelines remain high despite a paucity of data supporting their efficacy.[42] Few studies examining the relationship between methods of developing and disseminating guidelines and their effects on physicians' practices and patients' outcomes have been reported. Interest in guidelines remains strong, however, because "purely financial approaches to health care cost-control run the risk of decreasing spending on appropriate, as well as inappropriate services."[10(p222)] Proponents contend that well-designed guidelines will increase quality and reduce net costs of health care, but little is known regarding their potential to reduce overall health care costs.

Adverse consequences of implementing guidelines have not been adequately assessed. In particular, the contention that guidelines will discourage physicians from applying new technologies and interventions that are appropriate to an individual patient but absent from the relevant guidelines should be empirically evaluated. It is also important to assess whether the development of guidelines will be able to keep pace with rapidly changing areas of medicine. Additional experience with guidelines and more research are needed before their manifold effects can be predicted with accuracy.

Guideline development in the 1990s is likely to continue unabated in both the public and private sectors as pressures mount to contain costs and improve the quality of care. Guidelines will undoubtedly play some role in health care reform, although the precise nature of that role is currently a matter of speculation. Many experts caution that guidelines are not a panacea for all that ails the health care system. Considerably more research is needed before the full potential of clinical guidelines can be realized.

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* * *

CHRONIC CONDITION

Two failures.
Then a third.
A fuss of tubes.

After the doctor is called,
he disappears
between my legs.

The catheter's
rubber lip
inserted into me

inch by inch
burns,
an unrelenting pressure,

the tip pushed
deeper and deeper
until it enters,

the bladder's crypt
opening
for this thief

who picks the lock
of my privacy
and smiles,

not noticing
my voice
change pitch

panic
chasing across the years
to find a child

crouched on the floor,
something pulled
from a drawer,

a baffled scream,
nothing more.
Blood drains from my face

as I rush back to the place
where my body stops
being part of me,

and I look down
over myself
at a stranger's legs

being stretched apart.
When it's over
I put on my clothes

no longer a girl.
The moon's untouchable scar
hovers

outside my window.
I can barely follow
the doctor's anesthetic words

the bandage he offers,
all the treatments
he has not tried.

FRANCINE STERLE©
Iron, Minnesota

Articles

Restaurant Noise, Hearing Loss, and Hearing Aids

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Our multidisciplinary team obtained noise data in 27 San Francisco Bay Area restaurants. These data included typical minimum, peak, and average sound pressure levels; digital tape recordings; subjective noise ratings; and on-site unaided and aided speech discrimination tests. We report the details and implications of these noise measurements and provide basic information on selecting hearing aids and suggestions for coping with restaurant noise.

(Lebo CP, Smith MFW, Mosher ER, et al: Restaurant noise, hearing loss, and hearing aids. West J Med 1994; 161:45-49)

Restaurants are not merely eating and drinking sites; they are also popular settings for important social and business conversations. For the more than 27 million Americans with impaired hearing, restaurant noise can be debilitating. Hearing loss is ranked fourth among chronic medical conditions affecting Americans aged 65 and older. More than 3 million Americans wear hearing aids. Hearing impairment affects one in ten Americans. By age 50, 20% of Americans have a hearing loss.[1,2]

Existing disability statutes in the United States do not yet require noise control in restaurants, but it has been reported that the US Department of Justice, under the Americans With Disabilities Act of 1990, has taken the position that compliance with this legislation entails providing quiet listening areas in restaurants and other places in which hearing-impaired persons may convene. A report on this subject by the US Department of Justice is scheduled for early release.

Although persons with normal hearing do experience hearing difficulties in restaurants, the inability to understand speech in noisy restaurants may be a symptom of undiagnosed hearing loss. Poor speech discrimination in social groupings or in restaurants can become so frustrating that many otherwise active and healthy hearing-impaired adults tend to avoid outside dining and social activities.

Several years ago, two of us (E.R.M. and S.J.J.) initiated the use of a questionnaire for hearing-impaired adults to identify difficult listening environments and important listening situations ("Patient Satisfaction Survey," unpublished data, February 1993).[3] The results of this ongoing survey indicate that more than 80% of this group is dissatisfied with its ability to hear and understand conversation in restaurants, both with and without hearing aids. Restaurants are also listed as one of the four most important listening situations by more than 60% of those surveyed.

The most common type of acquired hearing impairment is sensorineural hearing loss, the principal causes of which are aging and noise-induced inner ear damage. Persons so affected hear better in quiet settings than in noisy ones. To address patients' speech intelligibility requirements in noise, audiologic procedures were modified to include quantitative measurements of unaided and aided sound-field speech discrimination in varied noise conditions with different speech stimuli and "real-ear" measurements (taken with a probe microphone placed in the external auditory canal). These test data were integrated into decisions regarding hearing aid selection and earmold configurations. Evaluation of an extensive patient database revealed that speech discrimination problems in noise are not adequately ameliorated by the types of hearing aids most commonly provided for them: linear circuitry and an in-the-ear or in-the-canal configuration. Currently, such hearing aids are routinely dispensed without testing their performance in background noise.

The US Food and Drug Administration has recently charged six major hearing aid companies with excessive or unsubstantiated advertising claims regarding the extent to which their products help users hear amid noise ("Technology and Health," *Wall Street Journal,* April 27, 1993, p 6; Associated Press (on-line), April 26, 1993, 1629 EDT, V0122).[4] Restaurants, sports events, and theaters were mentioned as areas where hearing aids do not perform in accordance with advertising claims.

Objectives

This study was designed to measure specific noise and

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relevant interior design features in restaurants of various types, evaluate hearing-aid performance in the presence of restaurant noise, and make digital tape and compact disc recordings of restaurant noise for clinical use.

Patients and Methods

A multidisciplinary research team consisting of two otologists, one audiologist, two architects, two acoustical engineers, and one communication scientist was assembled. We selected 27 San Francisco Bay Area restaurants to include all major restaurant types. A multiparametric measurement protocol was developed to describe the acoustic characteristics of restaurants.

Restaurant acoustic evaluations, sound pressure level measurements, subjective noise evaluations, digital tape recordings, and both aided and unaided speech discrimination tests were conducted by this team during peak eating times (with management consent) on Friday and Saturday nights. In addition to the calibrated measuring and recording hardware used by our acoustical engineers, an inexpensive type 3 sound-level meter (calibrated before use) was used for comparable measurements (decibels on the A and C slow scale) by another member of the team.

The measurements included A- and C-weighted maximum, minimum, and integrated (average) noise in various areas of each restaurant. The minimum noise sampling time was five continuous minutes. Each team member subjectively rated the intensity of restaurant noise using a scaled evaluation form. All measurements, observations, and tests were conducted almost simultaneously. Data were either recorded on site and saved by computerized measuring equipment or entered into a portable computer database immediately after exiting each restaurant.

A male subject with age-related hearing loss (it was not feasible to bring a statistically representative group of hearing-impaired subjects into these restaurants) was used to evaluate the performance of certain hearing aids in restaurants. This subject was fitted binaurally with behind-the-ear hearing aids equipped with both linear and nonlinear, multiband compression circuitry. A user-operated switch controlled the type of amplification in use. Aided and unaided speech discrimination testing was conducted in each restaurant, using a supplemented Harvey Gardner three- to four-syllable high-frequency word list.[5,6] Two subjects with normal hearing were used periodically to establish speech discrimination baselines.

The single-subject on-site evaluation of hearing aid performance in restaurant noise was expanded with more extensive sound-booth studies and real-ear measurements involving 57 subjects, using the same nonlinear, multiband compression, behind-the-ear hearing aids, standard noise tapes, restaurant noise recordings on compact discs, and other audio material recorded during the restaurant visits.

Spectral analyses of digital audio recordings and real-ear measurements of the hearing aids used were completed later using a FONIX 6500 (Frye Electronics) test set.

Results

This study generated a massive amount of multiparametric data. Because this article focuses on otologic and audiologic aspects of those measurements, only data germane to these concerns are included.

Noise Profiles of Restaurants

The range of A-scale-decibel (dBA) sound-pressure levels in our restaurant samples was wide. The average loudness ranged from 59 to 80 dBA sound-pressure levels (Table 1). The mean loudness level in all restaurants surveyed was 71 dBA sound-pressure levels, and the median was 72 dBA sound-pressure levels.

The average loudness level of 71 dBA sound-pressure levels is particularly important because it exceeds the average intensity of conversational speech (65 dB). Because speech intelligibility varies directly with the signal-to-noise ratio, the latter measurement is useful in evaluating the suitability of these restaurants for personal communication. Speech intelligibility requires a signal-to-noise ratio of +6 for persons with normal hearing and +12 for persons whose hearing is impaired.[7]

We classified the evaluated restaurants in terms of average noise level and signal-to-noise ratios as follows:

- *Type 1.* Less than 65 dBA; signal-to-noise ratio = 0: 6 restaurants. Quiet atmosphere with (designed or unplanned) acoustical serenity.
- *Type 2.* 65 to 74 dBA; signal-to-noise ratio = ≤10: 15 restaurants. High variability of speech intelligibility in both normal and hearing-impaired subjects.
- *Type 3.* 75 or more dBA; signal-to-noise ratio = >10: 6 restaurants. High ambient noise levels with or without music; conversation difficult for patrons with normal hearing and poor to impossible for persons with hearing losses.

Noise crested (peaked) as high as 87 dBA in some of the restaurants studied. It is important to note that the crest factor (the peak sound-pressure level minus the root-mean-square sound-pressure level during a stated time period) in restaurant noise is as critical as the average sound-pressure level because these noise peaks disrupt the ability of a listener to concentrate and to process speech effectively.[8] High crest factors tend to overload hearing aid amplifiers, with resultant signal distortion. They tend to cancel key speech consonant sounds, there-

TABLE 1.—*Ranges of Background Noise Levels in Restaurants Included in This Study*

Restaurant Types	*Decibels (dB) on the A Scale*
Bistro	65-80
California cuisine	74-80
Elegant	60-66
Ethnic	70-76
Family	59-70
Fast food	75-77
Steak	66-70

by reducing speech intelligibility. Restaurants with dramatically fluctuating noise levels present serious difficulties for patrons whose hearing aids require manual (local or remote) volume adjustments.

Independent Subjective Noise Evaluations

To establish how accurately diners might appraise loudness levels without the benefit of electronic measuring equipment, each member of the team rated each restaurant for loudness, using a five-point scale. These subjective appraisals correlated well with electronic acoustic measurements ($r = .88$).

Noise and Restaurant Types

Although the Zagat restaurant surveys list 32 restaurant types,[9] we deemed seven classifications to be adequate for our purposes: bistro, California cuisine, elegant, ethnic, family, fast food, and steak.

We found that restaurant classifications do not reliably predict loudness levels (Table 1). Elegant restaurants tended to be quiet, and bistros tended to be noisy, but there were exceptions. Such classifications, ours included, do not generally include ambient noise levels in their definitions. We found no correlation between price or food ratings and noise levels.

Acoustic and Architectural Design Factors

Restaurant profiles were compiled using the following variables: location (street type and traffic), building site access (distance to street, proximity to parking), occupancy (maximum seating, percentage of occupancy, actual numerical occupancy), environment (dining, reception, and bar areas, music and ancillary rooms) and dining room configuration (size, volume, walls, percentage of glass, ceiling material and height, flooring material, chair and table type and covering, booth type and covering). Although certain materials and architectural design features help control ambient noise, it is difficult to predict the interior ambient noise conditions accurately by means of these architectural features alone ("Best Meals, Best Deals," *Consumer Reports* 1992; 57:356-372).

Hearing Aid Performance

Our hearing-impaired subject (moderately severe, binaural, high-frequency hearing losses) was tested in all studied restaurants with Audiotone MSP-90C (Bausch & Lomb) behind-the-ear hearing aids, which are equipped with a switch that permits the user to select either the linear or the multiband compression circuitry. These aids were fitted with special nonoccluding Micro Ear ear molds, which are fabricated from Polysheer II, a polymerized vinyl compound made specifically for Pacific Coast Laboratory, San Leandro, California. These open ear molds have long, thin-walled ear canal tubes (usually 4 mm in external diameter) to avoid feedback (Figure 1). They permit the entry of nonamplified low-frequency sound into the ear canal in a normal manner and free the wearer from occlusion effects (the sensations caused by

Figure 1.—A typical Micro Ear behind-the-ear ear mold is shown. Note the length of the ear canal tube.

occluding the external auditory canal), including amplification of the user's voice by a hearing aid, foreign body awareness, acoustic effects, and attenuation. Amplification of the user's voice by hearing aids causes the user to reduce, rather than increase, vocal loudness in noise, causing hearing problems for the user's companions.[2,10,11]

The three- to four-syllable high-frequency words described previously were presented by the same speaker to the hearing-impaired subject to assess speech discrimination unaided and using both linear and multiband compression amplification. To evaluate the communication difficulties further, two team members with normal hearing also underwent the speech discrimination tests under identical conditions (in 11 restaurants only). The hearing-impaired subject's aided and unaided performances were compared in 11 restaurants. Surprisingly, the subject's unaided discrimination scores were higher than aided scores with linear amplification in 9 (45%) and equal in 1 (9%) of the studied restaurants. Unaided scores were never higher than those obtained when multiband compression amplification was used.

The performance of the multiband compression mode in the restaurant environment was substantially better than that obtained with linear amplification. The linear scores were poorer than those recorded with multiband compression in 18 of 27 restaurants (67%), equal to the multiband compression scores in 9 of the latter (33%), and better in none.

Discussion

The ambient noise levels in the restaurants studied varied greatly. There was an 18-dBA range in average loudness among the restaurants studied. Noise levels variably interfered with conversation, ranging from no interference to almost total masking. Speech discrimination testing of subjects with normal hearing and one hearing-impaired person indicated these masking effects can confound persons with normal hearing as well as those with impaired hearing. The critical background noise level for speech discrimination occurs between 65 and 70 dBA and corresponds with a signal-to-noise ratio of 0 dB.[12,13] When background noise levels exceed this level, it becomes in-

creasingly difficult for both normal and hearing-impaired persons to communicate.[14]

Our restaurant measurements showed substantial variability in loudness characterized by continual dynamic shifts that, whether caused by music, voices, floor noise, food service, or combinations thereof, erode speech discrimination. Within a given restaurant, the dBA sound-pressure level can vary with seating location and occupancy level; communication is easier in certain locations and is enhanced by low occupancy. Small, crowded rooms, however, can intensify noise levels. The headwaiters (or seating hosts) we encountered had mixed levels of awareness of the locations of the quietest areas or tables in their establishments.

Both our field test data and laboratory test data obtained with our restaurant recordings indicate environmentally that, for speech discrimination in restaurant noise, linear amplification is inferior to nonlinear amplification combined with adaptive multiband compression. This conclusion is supported by the aforementioned 57-subject study, which used the same hearing aid technology and employed both sound field and real-ear measurements of aided performance in noise.[3]

We encountered differences in hearing aid and subjects' performance with changes in background noise levels. The compression spectrum of the hearing aid (and the functional limitations thereof) and the specific settings of the circuitry are critical to any person's aided performance in noise. Ear-mold configuration is another variable that can greatly affect performance in noise. For the single subject in this study, some of the aided discrimination scores recorded in the noisiest establishments were better than others obtained in less noisy restaurants; this difference appears to be related to the compression and multiband characteristics of the hearing aids tested. In the 57-patient group study, many subjects showed drops in aided performance when the signal-to-noise ratio remained at −10, but the loudness levels increased by 10 dBA. Aided performance at higher noise levels was sometimes improved by changes in the compression settings or ear-mold configuration.

Recommendations

Ear examinations, including audiologic tests, are indicated in persons who admit to or are reported to have difficulty understanding conversations in restaurants. Untreatable hearing losses, of which the most common are the sensorineural type, can be mitigated with the appropriate hearing aids.

The following suggestions will be helpful to all persons wishing to converse effectively in restaurants:

- Ask for a quiet table;
- Do not sit near the kitchen or the walls, bar, or bus or waiter stations;
- Think "soft"—that is, patronize restaurants with plush environments (rugs, wall coverings, tablecloths, plants);
- Avoid restaurants providing live or recorded music;
- Avoid crowded places, especially small rooms, and periods of peak occupancy.

Fitting protocols for hearing aids and evaluations of their performance should better reflect the context of hearing-aid use. Speech testing, not just pure-tone testing, is essential. Unaided and aided sound-field speech discrimination tests in both quiet and noise should be used routinely in selecting and dispensing hearing aids to verify their appropriateness and effectiveness. Because the spectral characteristics of noise vary, hearing-aid performance should be evaluated using compact disc recordings of the environments in which a person routinely functions.

Binaural behind-the-ear hearing aids that are nonlinear, adaptive, and are equipped with multiband compression circuitry and soft, deep, nonoccluding or maximally vented continuous flow amplification ear molds are currently the hearing-aid system of choice for patients with high-frequency sensorineural hearing losses who need to understand speech, not just in quiet, but also in noise.

Equivalent hearing aid performance in noise cannot be expected for all patients with any given hearing aid technology. Patient expectations must be realistic; counseling by a physician and the support of family members are essential. Judgments of any improvements in speech discrimination must be relative to the medical and audiologic nature of the hearing loss as well as the age, lifestyle, motivation, and cognitive capacity of the patient.

The hearing aid industry, driven by intrinsic economics rather than social responsibility, is generally not (despite advertising claims) marketing hearing aids that incorporate the more important currently available technologic advances. Because physicians must assume ultimate responsibility for maximizing the benefits of hearing aids provided for their patients, it is incumbent on them to be aware of and demand state-of-the-art technology from the hearing aid industry and optimal evaluation, fitting, and follow-up services by audiologists and dispensers. The hearing aid industry should be urged to tailor compression spectra to real-world environments (perhaps to the restaurant noise models) and to develop both internal electronic adaptability and user-controllable variability in compression features. Until the major limitations and defects of the linear in-the-ear configuration can be eliminated, the industry would better serve the public by improving, promoting, and creating demand for high-technology behind-the-ear aids.

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Conferences and Reviews

Cardiac Evaluation and Risk Reduction in Patients Undergoing Major Vascular Operations

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Occult coronary artery disease often accompanies symptomatic peripheral vascular disease and has an important effect on survival. Most perioperative and late fatalities after peripheral vascular operations are due to cardiac causes. Noninvasive cardiac testing can identify patients at increased risk for postoperative cardiac complications, although controversy exists regarding the optimal preoperative evaluation. Risk reduction strategies for patients known to be at high risk are also controversial. Some authors advocate coronary revascularization with coronary artery bypass grafting or percutaneous transluminal coronary angioplasty before the vascular procedure. Others believe that the combined morbidity and mortality of 2 operations exceed those of a peripheral vascular operation performed with aggressive monitoring and medical therapy. Continuous electrocardiographic monitoring after an operation has identified silent myocardial ischemia as a powerful predictor of cardiac complications. Ongoing research is likely to provide insights into the pathogenesis of postoperative cardiac complications and may lead to specific therapeutic interventions. Few prospective studies have been done in this area, and the threshold for preoperative and postoperative intervention is unknown. I review the literature and present an algorithm to guide cardiac testing and risk reduction in patients undergoing elective vascular surgical procedures.

(Potyk DK: Cardiac evaluation and risk reduction in patients undergoing major vascular operations. West J Med 1994; 161:50-56)

Atherosclerosis has a direct pathogenic role in occlusive peripheral vascular disease and an indirect role in the development of vascular aneurysms.[1] Atherosclerosis is a diffuse process, and patients with peripheral vascular disease often have coronary artery disease. These patients frequently do not have symptoms of coronary ischemia because their lower extremity claudication limits exercise tolerance and prevents them from attaining cardiac stress levels that provoke ischemia. Therefore, preoperative cardiac assessment in this high-risk group can be difficult. In this article I review the relationship between coronary artery and peripheral vascular disease, noninvasive cardiac testing to identify patients at high risk for postoperative complications, and strategies that may decrease the incidence of cardiac complications following peripheral vascular operations.

Relationship Between Coronary Artery Disease and Peripheral Vascular Disease

To define the relationship between coronary artery disease and peripheral vascular disease, 1,000 patients being considered for peripheral vascular reconstruction at the Cleveland (Ohio) Clinic underwent preoperative coronary angiography. Coronary artery disease was surprisingly common; only 14% of those studied had normal coronary arteries. Patients clinically suspected of having coronary artery disease had a 78% incidence of "severe" coronary occlusion (greater than 70% stenosis of at least 1 vessel). Patients with no clinical evidence of heart disease had a 49% incidence of "moderate" coronary artery disease (stenoses of as much as 70%) and a 37% incidence of "severe" disease.[2-4] Several other studies have correlated coronary angiographic findings with different types of peripheral vascular disease. Patients with abdominal aortic aneurysms have a 52% to 82% incidence of severe coronary artery disease (75% to 100% occlusion of a major vessel), and those with peripheral occlusive disease have a 47% to 60% incidence of severe coronary artery disease. Many of these patients had no clinical evidence of cardiac disease, and 30% of those with severe coronary disease had normal electrocardiograms.[5,6] The high prevalence of occult coronary artery disease accounts for a substantial portion of both early and late postoperative deaths. Among patients undergoing resection of an abdominal aortic aneurysm and aortoiliac reconstruction, early deaths due to cardiac causes occur in 45% and 67%, respectively. Long-term follow-up reveals that cardiac disease is also responsible for 38% to 55% of late deaths in both groups.[7,8] A recent study in which a fifth of patients leaving the hospital after a vascular oper-

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ABBREVIATIONS USED IN TEXT

CABG = coronary artery bypass grafting
CASS = Coronary Artery Surgery Study
MI = myocardial infarction
PTCA = percutaneous transluminal coronary angioplasty

ation had cardiac complications within the next two years emphasizes these long-term cardiac complications.[9]* This is consistent with the 20% cardiac mortality over 11 years reported earlier.[7]

Cardiac Risk Assessment With Noninvasive Cardiac Testing

Cardiac risk stratification to identify patients at increased risk for postoperative complications is imperative before major vascular procedures. Preoperative cardiac catheterization is too invasive and expensive to be used in the initial assessment. The use of risk stratification based solely on clinical risk factors, such as the Goldman Multifactorial Index, has been advocated, but several studies show that these assessments may underestimate the incidence of cardiac complications after vascular surgical procedures.[10-15] Routine exercise treadmill testing is suboptimal because claudication limits exercise tolerance, resulting in inadequate stress levels and nondiagnostic studies.[16-17] Therefore, there has been a search for noninvasive techniques capable of identifying high-risk patients who may benefit from further invasive diagnostic studies and possible revascularization.

Measuring the left ventricular ejection fraction has been proposed as a method to identify high-risk patients undergoing vascular operations. As a functional assessment, the ejection fraction was thought to predict how well the heart could withstand the stresses of aortic cross-clamping and unclamping. In a 1985 study, patients with ejection fractions greater than 55% were reported to be at low risk for postoperative myocardial infarction (MI), whereas those with ejection fractions of less than 35% had a 75% incidence of postoperative MI.[18] More recent studies have shown that patients with ejection fractions of less than 35% can undergo a major vascular operation with acceptable 30-day mortality, while others have shown no correlation between the ejection fraction and the incidence of postoperative MI.[19-21] Prospective studies comparing ejection fraction determinations with dipyridamole-thallium imaging before aortic operations have shown ejection fractions to be inferior in predicting postoperative cardiac events.[14,22] Thus, the ejection fraction should not be used as the primary tool to identify high-risk patients before vascular procedures. The ejection fraction can, however, be used as an adjunct in the evaluation of certain patients. For instance, patients with ejection fractions of less than 30% are at risk for congestive heart failure, have limited survival, and should undergo a major vascular surgical procedure in only the most dire circumstances.

*See also the editorial by D. T. Mangano, PhD, MD, "Perioperative Cardiac Morbidity—Epidemiology, Costs, Problems, and Solutions," on pages 87-89 of this issue.

Using continuous electrocardiographic monitoring, several studies have documented a high frequency of perioperative myocardial ischemia. In patients with peripheral vascular disease, preoperative myocardial ischemia is predictive of postoperative cardiac events.[23,24] In one study, patients with preoperative ischemia had a 38% incidence of postoperative cardiac events whereas those with no preoperative ischemia had a 0.7% incidence of postoperative cardiac complications.[23] Other investigators examining the incidence of both preoperative and postoperative ischemia have found that postoperative myocardial ischemia is more strongly predictive of postoperative clinical events.[25,26]

Many authorities regard dipyridamole-thallium scintigraphy as the best test to predict adverse cardiac events in patients undergoing vascular operations. Dipyridamole induces coronary vasodilation, dilating normal vessels to a greater extent than atherosclerotic vessels, creating a coronary steal syndrome. Two images showing myocardial thallium distribution are compared: one immediately after dipyridamole is administered and the second hours later. A fixed defect—seen on the first image and persisting on the delayed image—is indicative of nonviable myocardium, usually the result of infarction. Thallium redistribution—a defect on the first image that fills in on the delayed image—is a marker for hypoperfused viable myocardium. The finding of thallium redistribution is associated with postoperative cardiac complications.

Dipyridamole-thallium scans were done on 48 patients with suspected stable coronary disease who were undergoing vascular operations. Eight of these patients (17%) had postoperative cardiac ischemic events. When comparing the dipyridamole-thallium results with clinical variables, the scan was the best predictor of postoperative myocardial infarctions. Patients with thallium redistribution had a 50% incidence of cardiac events, but no such events occurred in patients whose scans were normal or showed persistent defects.[27] In another study, preoperative dipyridamole-thallium scans were taken of 116 patients referred for aortic reconstruction. In all, 54 patients showed evidence of thallium redistribution; of these, 9 (17%) had postoperative myocardial infarctions. None of the 62 patients with normal studies or persistent defects had postoperative myocardial infarction or cardiac death.[28] Recent studies, however, have questioned the usefulness of preoperative dipyridamole-thallium scans. In one study, a 40% incidence of cardiac complications and 6% mortality were reported in patients whose preoperative scan showed fixed defects. Further stratification of patients with fixed defects has been advocated by obtaining a delayed image four hours after the second scan. If the fixed defect subsequently fills in, the patient would be considered to be at increased risk for cardiac complications.[14] In another study of 60 patients undergoing elective vascular operations, each patient had preoperative dipyridamole scans, postoperative monitoring with continuous electrocardiography, and postoperative clinical assessment. There was no association between thallium redistribution and the incidence of perioperative ischemia or

adverse cardiac outcomes. The sensitivity and specificity of dipyridamole-thallium scans for clinical events were 46% and 66%, respectively.[29] Quantitative dipyridamole imaging has been reported to identify high-risk patients more accurately, although this technique is not widely used.[30-32]

Despite these conflicting reports, dipyridamole-thallium scintigraphy is the most commonly used tool to assess cardiac risk before a peripheral vascular operation. Several questions have been raised regarding the use of these scans: Should every patient have a dipyridamole scan before surgical therapy? and Can scan performance be improved through better patient selection?[33] A retrospective analysis found five clinical factors that enhanced the predictive value of dipyridamole scans: age greater than 70 years, a history of angina, the presence of diabetes mellitus, Q waves on the resting electrocardiogram, and a history of ventricular arrhythmias. Patients with none of these clinical risk factors had a 3% incidence of cardiac complications after a major vascular procedure. Patients with three or more risk factors had a 50% incidence of postoperative cardiac events. Even patients with three or more risk factors whose scans were normal had a 30% incidence of postoperative complications. The scan was most discriminating in patients with one or two risk factors. In this group a normal scan or a fixed defect was associated with a 3% incidence of cardiac events, whereas thallium redistribution was associated with a 30% incidence of postoperative events. It was recommended that only patients with one or two clinical risk factors have preoperative dipyridamole-thallium scans. Those with no clinical risk factors were thought to be at low risk and to be able to proceed directly to surgical therapy. Those with three or more risk factors should be considered to be at increased risk for postoperative cardiac events and should be considered for further workup.[34]There are currently no prospective studies reporting the selective use of dipyridamole-thallium scans. A retrospective series of 200 elective aortic reconstructions was reported in which thallium scans were ordered at the discretion of the referring physician or surgeon. Preoperative scans were done in 29%, prompting coronary angiograms in 11% and coronary revascularization in 9%. These interventions resulted in an operative mortality of 2% and cardiac morbidity of 4%.[35] Based on the available data, a selective approach to screening patients seems reasonable, but validation with prospective studies is necessary.

Some institutions have replaced dipyridamole-thallium scans with adenosine-thallium scans, dipyridamole-sestamibi scans, or dipyridamole or dobutamine echocardiography. Adenosine is a short-acting coronary vasodilator that has fewer side effects than dipyridamole.[36] Adenosine-thallium scanning has been shown to be equivalent to exercise thallium scintigraphy in the diagnosis of coronary artery disease, but it has not been compared with dipyridamole-thallium scanning.[37] Technetium Tc 99m sestamibi is a new myocardial perfusion agent that offers superior quality images when compared with the use of thallium and also adds additional information with simultaneous ejection fraction determinations. Data suggest that ^{99m}Tc-sestamibi will be useful when combined with either dipyridamole or adenosine.[38] Dipyridamole and dobutamine echocardiography have also been reported to identify patients at increased risk for cardiac complications.[39,40] Arm exercise coupled with thallium imaging can also diagnose coronary artery disease in patients with peripheral vascular disease.[41] These techniques require further study before their routine use is recommended.

Strategies to Decrease Postoperative Cardiac Complications

The diagnostic studies discussed earlier permit the identification of patients at increased risk for perioperative cardiac events when undergoing major vascular operations. Once a patient is determined to be at high risk, risk reduction strategies should be considered. The options for reducing risk include a coronary artery bypass grafting (CABG) operation before the vascular procedure, percutaneous transluminal coronary angioplasty (PTCA) before the vascular procedure, or aggressive monitoring directing medical interventions before, during, and after the operation. Few prospective data are available in this area.

Several authors have reported minimal complications in patients who have undergone a CABG procedure and then later were seen for a noncardiac operation (Table 1).[42-51] A total of 1,600 patients enrolled in the Coronary Artery Surgery Study (CASS) registry, who subsequently required noncardiac operations, were analyzed. Patients were separated into three groups based on their coronary angiograms and their subsequent treatment: patients without substantial coronary artery disease, those with coronary disease who underwent CABG, and those with notable coronary artery disease who were managed with medical therapy. Surgical mortality following noncardiac operations was then determined for each group. Patients without coronary artery disease had an operative mortality of 0.5%. Patients with considerable coronary occlusions who had CABG before the noncardiac procedure had an operative mortality of 0.9%, and those patients with coronary artery disease who received medical therapy had an operative mortality of 2.4%.[44] In another study 60 patients with previous CABG who later presented for major surgical therapy were reported; there were no perioperative deaths and only 8 transient arrhythmias.[52] These studies reflect noncardiac operative mortality that is considerably lower than that associated with vascular operations. A 1.6% mortality was reported after aortic aneurysm repair in patients who had previously undergone bypass grafting, whereas patients without previous CABG had a 4.8% mortality.[45] Other groups have reported no mortality and no postoperative MIs in patients who had CABG before major vascular operations.[43,53]

These results are often cited as arguments in favor of recommending CABG before vascular operations to decrease perioperative cardiac complications. These studies, however, do not address the value of CABG because of their inherent selection bias. Patients were enrolled in

TABLE 1.—*Operative Mortality With and Without Specific Interventions*

Source	Patients, No.	Population	Intervention	Mortality, %
Gersh et al, 1983[42]	1,086	<65 years old	CABG alone	1.9
		>65 years old	CABG alone	5.2
		>75 years old	CABG alone	9.5
Toal et al, 1984[43]	224	Peripheral vascular disease	CABG alone	6
Foster et al, 1986[44]	1,600	Without CAD	None, NCS	0.5
		With CAD	NCS with previous CABG	0.9*
		With CAD	NCS with medical therapy	2.4*
Young et al, 1986[45]	302	Peripheral vascular disease	CABG alone	6
			Abdominal aortic surgery with previous CABG	1.6*
			Abdominal aortic surgery without previous CABG	4.8*
Isaacson et al, 1990[46]	40	Abdominal aortic surgery	Central venous pressure monitoring	0†
			PCWP monitoring	2†
Mullany et al, 1990[47]	159	>80 years old	CABG alone	10
		>80 years old with peripheral vascular disease	CABG alone	17
Allen et al, 1991[48]	148	With CAD	NCS with previous PTCA	1*
Berlauk et al, 1991[49]	89	Vascular surgery	Central venous pressure monitoring	9.5
			PCWP monitoring	1.5
Taylor et al, 1991[50]	491	Vascular surgery	5% underwent preoperative cardiac evaluation	2.2
Huber et al, 1992[51]	50	With CAD	NCS with previous PTCA	1.9*

CABG = coronary artery bypass surgery, CAD = coronary artery disease, NCS = noncardiac surgery, PCWP = pulmonary capillary wedge pressure, PTCA = percutaneous transluminal coronary angioplasty

*Mortality of the noncardiac operation, not including mortality of the intervention. †Not statistically significant.

these studies when they presented for their second surgical procedure. All patients had survived their CABG and were considered candidates for a second major operation. If CABG is recommended specifically to decrease the incidence of surgical complications, the morbidity and mortality of CABG should be included in the overall morbidity and mortality. A "prophylactic CABG" is done specifically to decrease postoperative complications and must be contrasted to a CABG done for indications that have shown survival benefit.[54]

Several reports document that patients with peripheral vascular disease have increased morbidity and mortality after CABG. The mean age of patients undergoing peripheral vascular operations is 65 years, and the CASS data have shown that CABG in this age group is associated with an increased number of complications. Mortality after CABG was 5.2% in patients older than 65 years, compared with 1.9% in younger patients. Mortality increased further to 9.5% in patients older than 75 years. Although morbidity was not reported, older patients had substantially longer hospital stays than younger patients.[42,55] Other studies have confirmed these results. In two separate reports, 6% CABG mortality rates were noted for patients with peripheral vascular disease.[43,45] Mortality from CABG in patients older than 80 years is 10% and increases to 17% in the presence of peripheral vascular disease.[47] Clearly patients with peripheral vascular disease are at greater risk for complications after CABG than other populations.

When considering prophylactic revascularization before a vascular operation, the cumulative morbidity and mortality must be examined. There are no prospective data, and historical information is difficult to interpret because of differences in patient populations and reported outcomes. Recognizing these limitations, the above data indicate that prophylactic CABG may increase overall mortality. Coronary bypass surgery in patients with peripheral vascular disease carries a 6% mortality, followed by vascular surgery with as high as 1.6% mortality (after CABG), resulting in 7.6% mortality. This figure is much higher than the 4.8% mortality in patients with documented coronary atherosclerosis who did not undergo CABG before a vascular procedure.[43,45] Therefore, in the absence of prospective data, information obtained by combining studies indicates that prophylactic CABG may increase rather than decrease mortality after a major vascular operation.

Percutaneous transluminal coronary angioplasty has been advocated as an alternative to CABG. It is associated with less morbidity and mortality than CABG, and its use has been advocated before major surgical procedures if substantial coronary artery disease is found. This recommendation is based on anecdotal experience because there is little information addressing the efficacy of PTCA before noncardiac operations. One report included 148 patients who underwent PTCA and later required noncardiac procedures. One cardiac death and seven ischemic events were reported in the postoperative period for an overall cardiac morbidity of 11%.[48] The Mayo Clinic (Rochester, Minnesota) reported a retrospective uncontrolled series of 55 patients who had PTCA before a noncardiac operation in an effort to diminish postoperative cardiac morbidity. Their postoperative myocardial infarction rate was 5.6%, and postoperative mortality was 1.9%.[51] The postoperative mortality of 1.9% may not be substantially different from the 2.4% mortality in patients undergoing noncardiac operations without previous revascularization.[44] The PTCA studies are retrospective and without control groups, so it is difficult to assess the effect prophylactic PTCA has on postoperative cardiac complications.

Efforts to decrease postoperative cardiac complica-

tions have recently shifted from preoperative revascularization to postoperative monitoring and aggressive medical therapy. The Perioperative Ischemia Research Group used continuous electrocardiographic monitoring before, during, and after noncardiac operations to study myocardial ischemia. The incidence of myocardial ischemia was 20% preoperatively, 25% intraoperatively, and 41% postoperatively. Postoperative myocardial ischemia had the strongest univariate association and the only multivariate association with clinical cardiac events. Although controversy exists regarding the relative importance of preoperative and postoperative ischemia, several reports have confirmed the strong association between postoperative ischemia and clinical cardiac complications.[25,56-58] Postoperative ischemia occurs within the first 48 hours after a surgical procedure and is more severe than ischemia detected during other periods. Postoperative myocardial ischemia is clinically silent more than 90% of the time, is not associated with tachycardia, and follows a circadian rhythm with most ischemic events occurring in the early morning hours.[25,26,59,60] One group has reported the presence of myocardial ischemia for 53 minutes before each clinical event.[24] Thus, monitoring high-risk patients for 48 hours may allow interventions that decrease the severity of ischemia. The physiology of postoperative myocardial ischemia is not well understood, but it does not appear to be a simple supply-and-demand phenomenon. Therefore, it is unclear which interventions will decrease the amount of ischemia and whether these interventions will translate into fewer clinical events. There have been preliminary reports that β-blockade and high-dose narcotic analgesia can decrease the postoperative ischemic burden.[61-63] These results are preliminary, and ongoing research is likely to provide further insights into postoperative myocardial ischemia—its pathogenesis, prevention, and treatment.

Even without specific postoperative interventions, several studies have reported decreasing mortality—on the order of 2%—after abdominal aortic aneurysm repair.[50,64,65] In addition, there are data supporting further declines in operative mortality when hemodynamic monitoring is used.[66,67] A recent prospective, randomized study used pulmonary artery catheters to test the hypothesis that preoperative "hemodynamic optimization" would result in fewer perioperative complications after peripheral vascular operations. Patients whose hemodynamic parameters were manipulated to obtain a normal cardiac index, pulmonary artery wedge pressure, and systemic vascular resistance before the surgical procedure were compared with a control group without invasive hemodynamic monitoring. The pulmonary artery catheter group had fewer adverse intraoperative events, less postoperative morbidity, fewer early graft thromboses, and fewer deaths. The overall complication rate was 16% in the pulmonary artery catheter group and 43% in the control group. No differences were detected between patients whose pulmonary artery catheter was placed 12 or 3 hours preoperatively, so the duration of preoperative optimization was not a factor.[49] Another group inserted pulmonary artery catheters preoperatively and then determined filling pressures that produced optimal left ventricular performance for each patient undergoing aortic aneurysm repair. The pulmonary artery wedge pressure was maintained at this optimum value during and after the operation. Using this protocol, the authors reported a hospital mortality of 0.9%, although there was no control group in this study.[68] These reports support earlier data indicating that aggressive hemodynamic monitoring in high-risk patients results in fewer cardiac complications.[69] Other data, however, leave this conclusion questionable. Patients undergoing abdominal aortic procedures have been randomly assigned to central venous pressure or pulmonary artery catheter monitoring. Two studies showed no differences in morbidity or mortality between these two modalities. Both of these studies included small numbers and enrolled only low-risk patients.[46,70] Pulmonary artery catheter monitoring may be beneficial when higher risk patients are included. Previous studies have shown that changes in pulmonary capillary wedge pressure are not always reflected by changes in the central venous pressure during aortic operations. Clinical variables could not identify those patients in whom the central venous pressure and pulmonary capillary wedge pressure were discordant. It was concluded that there was no substitute for measuring the pulmonary capillary wedge pressure.[71] The risks and benefits of pulmonary artery catheterization in surgical patients were addressed, and it was found that pulmonary artery catheter monitoring provided useful information while exposing patients to minimal risks.[72] Thus, pulmonary artery monitoring may not be necessary in low-risk patients, but has the potential to decrease morbidity and mortality in high-risk patients. Again, randomized prospective studies are needed.

Summary

Coronary artery disease often accompanies peripheral vascular disease and exerts an adverse effect on surgical outcome. Dipyridamole-thallium scintigraphy is currently the most widely used noninvasive technique for identifying high-risk patients before a surgical procedure, though it will be replaced by other techniques in the future. The management of high-risk patients remains controversial because of a lack of prospective data. The threshold for intervening with revascularization is not defined, but "consideration for vascular surgery alone is not an indication for coronary revascularization."[55(p210)] Revascularization should be considered, however, for patients in whom long-term benefit has been demonstrated.[54]

Based on the preceding literature review, the following modification of Wong and Detsky's approach to patients undergoing elective vascular surgical procedures is recommended (Figure 1).[73] Patients should have a complete history and physical examination. Eagle's clinical criteria—older than 70 years, history of angina, the presence of Q waves on the electrocardiogram, history of ventricular arrhythmias, and diabetes mellitus—can then provide guidelines for further evaluation. Because the evaluation of angina in patients with peripheral vascular disease remains problematic, only those patients able to walk two blocks at

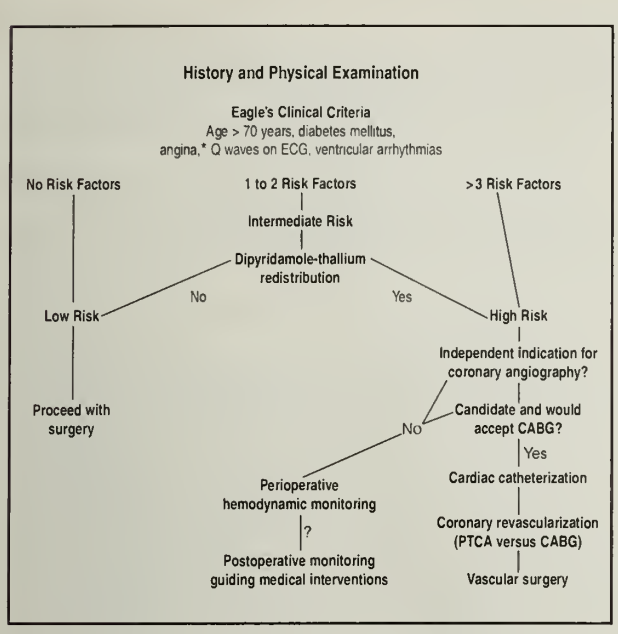

Figure 1.—The schema shows the cardiac evaluation and risk reduction before major vascular surgical procedures (modified from Wong and Detsky[73]). CABG = coronary artery bypass grafting, ECG = electrocardiogram, PTCA = percutaneous transluminal coronary angioplasty, * = patients unable to walk 2 blocks at a normal pace should not be considered free of angina

a normal pace (Canadian Cardiovascular Society Angina Class II or better) should be considered free of angina.[12,74] Patients with none of Eagle's risk factors are considered at low risk and may proceed directly to surgical treatment. Patients with one or two clinical risk factors are considered at intermediate risk and should undergo dipyridamole-thallium scintigraphy. Those with no evidence of thallium redistribution are considered at low risk and may undergo an operation. Patients whose scans show redistribution and those with three or more clinical risk factors are considered to be at high risk for cardiac complications. Because prophylactic CABG may increase morbidity and mortality and preoperative PTCA is of unproven value, most of these high-risk patients can be managed medically without preoperative revascularization. Invasive cardiac evaluation should be limited to patients with independent indications for coronary angiography and to those who are candidates and are willing to undergo CABG before their vascular procedure. Patients identified as high risk should have a pulmonary artery catheter inserted and should have normal hemodynamic values before their operation. Every effort should be made to maintain values within the normal or optimal range during the intraoperative and postoperative periods. Clinicians should be aware of the high incidence of silent postoperative myocardial ischemia and its implications. Interventions such as patient-controlled analgesia and β-blockade may reduce the incidence of postoperative cardiac complications, but there are no data yet available to support their routine use.

Coronary artery disease has a profound adverse effect on the long-term survival of patients with peripheral vascular disease. All of these patients should be considered to have lifelong risks for cardiac complications and should be observed closely.

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Epitomes

Important Advances in Clinical Medicine

Preventive Medicine and Public Health

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The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in preventive medicine and public health. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Preventive Medicine and Public Health of the California Medical Association, and the summaries were prepared under the direction of Dr Thom and the Scientific Advisory Panel to the Section on Preventive Medicine and Public Health.

Escherichia coli O157:H7 Infections

ALTHOUGH *Escherichia coli* is a normally benign intestinal bacterium, certain strains cause diarrhea through several pathogenic mechanisms. In 1982 a restaurant-associated outbreak of bloody diarrhea resulted in the recognition of *E coli* O157:H7, the most common enterohemorrhagic serotype.

Escherichia coli O157:H7 causes diarrhea that is sometimes bloody and is often accompanied by severe abdominal cramps, vomiting, nausea, or a slight fever. In around 5% of persons with *E coli* infections, the hemolytic uremic syndrome develops, characterized by hemolytic anemia, thrombocytopenia, and temporary or permanent renal impairment. Asymptomatic infection is rare, but has been documented during outbreaks. Other complications are thrombotic thrombocytopenic purpura, unnecessary surgical intervention, coma or seizures, pancreatitis, and diabetes mellitus. A small percentage of symptomatic *E coli* O157:H7 infections are fatal.

The differential diagnosis of bloody diarrhea includes infections with *Shigella* species, *Campylobacter jejuni*, and *E coli* O157:H7. Because *E coli* O157:H7 requires special media and is not identified on routine stool culture, nonbloody diarrhea caused by the organism may go unrecognized. When a health maintenance organization in the Puget Sound area of Washington State screened all diarrheal stool specimens, *E coli* O157:H7 was identified as commonly as *Shigella* species, suggesting the organism is underdetected. Cultures for *E coli* O157:H7 may be negative if the stool specimen is obtained late in the course of the infection.

Beef, particularly incompletely cooked ground beef, is the most commonly reported food exposure in cases of *E coli* O157:H7 infection. Other foods associated with outbreaks include raw milk and items presumably cross-contaminated with raw beef. One outbreak was caused by cider made from apples collected from the ground in an orchard where cows roamed. Outbreaks have also been associated with contaminated drinking or swimming water. Secondary transmission has been found within families and in day-care centers. No outbreaks have been attributed to ill food handlers.

Although *E coli* O157:H7 infection is not reportable in most states, it has been reportable in Washington State since 1987. Each year in Washington there are about 300 sporadic cases of *E coli* O157:H7 infection, primarily the result of mishandling meat items at home. During the first two months of 1993, the state had a large *E coli* O157:H7 outbreak associated with a fast-food chain. There were 477 people with positive cultures or the hemolytic-uremic syndrome, including 52 (11%) secondary cases. Of the 477 patients, 144 were admitted to hospitals, the hemolytic-uremic syndrome developed in 30, and 3 died. Hamburger meat from the chain grew the outbreak strain.

Antimotility agents should not be given to a patient with *E coli* O157:H7 infection. Antibiotic treatment does not appear to affect the disease course. Some studies suggest a poorer outcome with the use of trimethoprim and sulfamethoxazole or gentamicin sulfate. Hydration should be maintained initially and the patient observed for evidence of anemia, thrombocytopenia, or acute renal impairment. The hemolytic uremic syndrome may develop within a week of the initial diarrheal symptoms, in which case fluid and electrolyte management is necessary, including prompt dialysis if anuria or oliguria develops.

Cooking meat completely and avoiding cross-contamination with raw meat will reduce the risk of infection with *E coli* O157:H7. When a case occurs in a family, strict sanitation is important. Exclusion from day care un-

til the infection is cleared was recommended during the Washington outbreak. As other states add infection with E coli O157:H7 to reportable disease lists, it will likely be reported in most of the country.

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Controversy in Clinical Cancer Screening—Mammography

MAMMOGRAPHIC SCREENING to detect curable breast cancer has become one of the most widely recommended and accepted procedures in clinical preventive medicine. Although its benefit is well established for women between the ages of 50 and 69, its routine use with younger women, increasingly common in the past decade, has recently been challenged by new data and by expert review.

Eight major randomized clinical trials have now been reported. None has shown survival benefit at five to seven years' follow-up for women screened at ages 40 to 49, and meta-analysis of combined results shows a nearly equal risk of breast cancer death among those screened and those not screened. One early trial suggests a lower mortality at 10 to 18 years' follow-up in the mammography group, but its statistics are disputed. There is methodologic controversy about each of the studies, but the cumulative weight of the evidence has led the National Cancer Institute to withdraw its previous recommendation for the routine screening of women aged 40 to 49 years. Monthly self-examination and yearly examination by a physician are still considered prudent for all women older than 40. The American Cancer Society has not changed its advisory that all women older than 40 be offered mammography.

Mammography tends to be less accurate in younger women. The lower breast fat content before menopause makes the breast less radiolucent and mammography less sensitive, with more chance of missing cancers and giving falsely negative results. Conversely, greater breast density before menopause increases the risk of misinterpreting local densities as possible neoplasms, making mammography less specific, with more falsely positive results. Lower sensitivity and specificity, combined with a lower prevalence of cancer, make it less likely that an abnormal mammogram in a younger woman will actually prove to be cancer. This lower predictive value of a positive test is the screening statistic of particular interest to clinicians who must advise the next step in evaluating a positive screening test. A recent report of a large screening program in the San Francisco Bay Area is instructive. Abnormalities seen on mammograms (requiring evaluation for possible cancer) among 40- to 49-year-olds had only a 1-in-25 chance of turning out to be cancer (a positive predictive value of 4%). The positive predictive value increased twofold in women aged 50 to 59 and fourfold in women aged 60 to 69. Women 40 to 49 years old with a family history of breast cancer had a positive predictive value (13%) three times that of others.

A history of breast cancer in a mother or sister at an early age provides the best current marker for an increased risk of cancer before age 50. A study of one large cohort found such women to be at a fivefold greater risk of fatal breast cancer. Genetic tests for this factor are being developed. Meanwhile, the growing reluctance to recommend routine mammographic screening of younger women should not deter its inclusion in clinical surveillance when family history indicates high risk.

Data are sparse for assessing the value of screening the increasing proportion of healthy women who are older than 70. The positive predictive value of mammography at this age, however, exceeds that of all younger age groups. The underrepresentation of older women in clinical trials should not exclude them from the benefits of early detection when clinically indicated.

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Controversy in Clinical Cancer Screening—Prostate-Specific Antigen

AS THE POPULATION has aged, prostate cancer has become the most commonly diagnosed cancer in men and the second most common cause of cancer deaths in men. That cancer confined to the prostate gland can be cured by radiation or surgical therapy provides strong incentive for early detection and perhaps screening. This is countered by the cancer's often indolent pattern of growth and metastasis and the morbidity associated with costly treatments. Thus, screening benefit decreases with age. The lifetime risk of prostate cancer developing in a 50-year-old man is estimated—from autopsy reports of its high prevalence in the elderly—as 42%, with only a 9.5% risk of clinical disease and a 2.9% risk of dying of prostate cancer. There are no data on the morbidity and mortality benefits of screening for prostate cancer comparable to those supporting routine mammography for breast cancer among women aged 50 to 70. A large trial is being developed, but results are 10 to 20 years away.

Assay of the prostate-specific antigen (PSA) has been increasingly advocated for detecting curable cancer, with a serum level greater than 4 μg per liter (4 ng per ml) generally taken as requiring further evaluation. The best estimates on PSA efficacy in the general screening of 50-

to 70-year-old men without known prostate problems suggest a sensitivity of about 67%, a specificity of about 82%, and a positive predictive value of about 43%. These values are higher than those found for digital rectal examination in the same study. This would generally be considered inadequate accuracy for a screening test. When both the digital rectal examination and PSA assay reveal abnormalities, specificity is increased but sensitivity falls to 33%, and the positive predictive value is only slightly increased (49%). Screening of only symptomatic men produces higher sensitivity but lower specificity. Strategies to make the test both more sensitive and more specific have been elusive. General screening with the PSA assay is thus likely to be expensive (in evaluating false-positive results) while still missing many cancers. While detecting and curing some cancers that would have been fatal, the balance of cost and benefit in such screening is unclear. One analysis suggests it would cost $12.7 billion a year to screen (with PSA tests), evaluate, and treat all American men aged 50 to 75 for prostate cancer. The cost per cancer death prevented would be four times that for mammographic screening.

Despite the American Cancer Society's conclusion that optimal cancer detection should include annual PSA testing for men older than 50, many others have urged caution in its routine use, and the United States Food and Drug Administration has approved PSA assays for use only in observing patients after diagnosis. Clinicians may achieve more efficient diagnostic aid from this imperfect but valuable test by using it selectively when specific symptoms, rectal examination findings, family history, or African-American ethnicity predict an increased risk. Preliminary data suggest that consistent annual increments in the PSA level (velocity), rather than a single elevated value, may provide a more physiologic and cost-effective criterion for pursuing the possibility of cancer. The only current certainty is that the PSA controversy will challenge physicians' skill in interpreting the ambiguities of science to newspaper-reading patients and to cost-conscious payers.

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Domoic Acid Poisoning

DOMOIC ACID POISONING is the newest threat to the seafood-consuming public. This bizarre syndrome is caused by the neurotoxin domoic acid, which may be concentrated by finfish or filter-feeding shellfish as they consume the unicellular algae that produces the toxin.

Domoic acid poisoning was first recognized in November 1987, after an outbreak of gastrointestinal and neurologic illness in Canadians who had eaten cultivated mussels from Prince Edward Island in eastern Canada. In this outbreak, more than 100 persons became ill with a syndrome characterized by nausea, vomiting, abdominal cramps, diarrhea, severe headache, confusion, loss of short-term memory, and a number of less common symptoms. In most cases, symptoms lasted a few days to a few weeks. The memory impairment was severe and in some cases permanent, and thus, the syndrome was originally called amnestic shellfish poisoning. The source of domoic acid in the mussels was determined to be an intense bloom of the diatom *Nitzchia pungens* the month before.

Domoic acid is a tricarboxylic amino acid that is classified as an excitatory amino acid (along with the dicarboxylic amino acids glutamic acid and aspartic acid). It acts through the inotropic non-NMDA receptor and especially affects the hippocampus and amygdala of the brain. The time from ingestion to intoxication can range from minutes to hours.

Since the original Canadian outbreak of domoic acid poisoning, public health monitoring data and some published studies have shown that domoic acid can be found in various other North American coastal waters. Domoic acid is of particular concern to the Pacific Coast states. The only method to determine if domoic acid poisoning is present is to test the shellfish.

In September 1991, an epidemic of domoic acid poisoning killed hundreds of brown pelicans and cormorants in Monterey Bay, California. No human illnesses were reported in this incident, but it was especially notable because it was the first documentation of domoic acid poisoning occurring outside of Atlantic Canada and the first documentation of domoic acid being found in herbivorous finfish (anchovies) and being produced by the phytoplankton *Pseudonitzschia australis*. Three species of *Pseudonitzschia* are now known to produce domoic acid.

In October and November 1991, an outbreak of domoic acid poisoning occurred in Washington State, affecting about two dozen people who had consumed razor clams. Shellfish testing determined that razor clams were contaminated at several locations along both the Oregon and Washington coasts, although mussels were almost entirely free of the toxin. It was later determined that Dungeness crabs from all along the Pacific Coast also were contaminated with domoic acid.

In the past two years, considerable sampling and other work has been done in an effort to define the biology and ecology of the phytoplanktons of concern, the extent of domoic acid contamination of West Coast shellfish, the ecologic determinants of domoic acid-producing diatom blooms, and the toxic effects of domoic acid, among other things. Many questions remain, but it is now clear that domoic acid may be found in a number of edible marine species all along the Pacific Coast of North America, as well as in eastern Canadian Atlantic waters and the Gulf of Mexico.

Clinicians should be alert to the occurrence of this new syndrome and notify public health authorities imme-

diately about the occurrence of any suspect cases. Of note, there is no antidote and treatment is supportive. Likewise, public health, food safety, and fishery agencies need to continue monitoring programs aimed at detecting contamination of fish or shellfish before the fish get into the channels of trade or are harvested by sport fishers.

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Gastric Adenocarcinoma and *Helicobacter pylori* Infection

GASTRIC ADENOCARCINOMA is the second most common cause of cancer death in the world. In the United States, however, where socioeconomic and hygienic factors have improved dramatically over the past half century, the incidence of gastric cancer has plummeted. From being the most common form of cancer in the 1930s, gastric cancer is now the ninth most common malignant neoplasm, affecting fewer than 10 per 100,000 persons per year. Studies of immigrant populations have provided clues to the events leading to the decline in the gastric cancer incidence. Persons who move from high-risk to lower-risk regions lessen their cancer risk only moderately, even if they immigrate at a young age. Second-generation immigrants, however, adopt a gastric cancer risk much closer to that of their new country. It has thus been inferred that an environmental factor is important in causing cancer and that this factor exerts its influence in childhood. Furthermore, it has been concluded that this risk factor is somehow related to socioeconomic conditions.

Recent data suggest that infection with a bacterium, *Helicobacter pylori* is a critical environmental factor in gastric carcinogenesis. *Helicobacter pylori* is a gram-negative rod that causes both gastritis and peptic ulcer disease. The organism, which had remained uncharacterized until the early 1980s, lives in a neutral pH niche between the mucous layer of the stomach and the gastric epithelium. There it produces large quantities of urease, cleaving urea into ammonia and protecting the organism from surrounding acid with a base cloud. *Helicobacter pylori* is never found remote from gastric epithelium and does not invade tissue. It is extremely common, infecting about 40% of the United States population. Infection rates increase with age and with low socioeconomic status. Once a person is infected, the organism remains in the stomach and is not eliminated without complicated antibiotic therapy.

Long before the "discovery" of *H pylori*, it was known that the stomach undergoes a sequence of histopathologic changes before cancer occurs. In chronologic progression, these "preneoplastic" conditions are superficial gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and finally cancer. Because *H pylori* is the clear causal agent in superficial gastritis, it is intuitive to suspect it would be linked to cancer. This pathologic association has been confirmed in numerous studies, including ecologic studies, case-control studies of cancer patients, and nested case-control studies within large cohort populations. The combination of studies provides convincing evidence that gastric cancer occurs in regions of high *H pylori* prevalence, that *H pylori* is more common in cancer patients than in controls, and that *H pylori* infection precedes the onset of cancer by many years. In prospective studies, infection increases the risk for cancer between threefold and sixfold. From this it has been calculated that 40% to 60% of gastric cancers would not occur if *H pylori* did not exist. Despite these powerful data, however, it must be recognized that infection with *H pylori* is common in all populations and that the overwhelming majority of infections will not result in cancer. Both the age at which infection begins (persons infected during childhood are at worst risk) and the site of infection within the stomach (corporal involvement is probably worse than antral infection only) may determine the degree of risk. Moreover, in many people, infection alone may not be sufficient to cause cancer unless combined with other cofactors, such as dietary nitrates or salt.

About 30% of cancers worldwide are now thought to be attributable, at least in part, to infectious agents such as schistosomes, *Clonorchis sinensis*, papillomavirus, hepatitis viruses, or Epstein-Barr virus. *Helicobacter pylori* is the first bacterium among these infectious pathogens to be associated with carcinoma. Although there are plausible mechanisms for *H pylori*-related carcinogenesis, final confirmation of a causal association awaits trials showing that curative antibiotics against *H pylori* prevent the development of cancer. Until then, the routine treatment of asymptomatic carriers to prevent cancer cannot be recommended.

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Domestic Violence

DOMESTIC VIOLENCE, spousal abuse, and battering are terms that refer to controlling behaviors between people in past or present intimate relationships. Children also often suffer physical and emotional trauma through domestic violence. Research has focused on the violence

perpetrated by men against women. Violence also occurs against men by women, among gay and lesbian couples, and to disabled or elderly persons, but the research in these areas is limited.

Violence against women by men is generally repetitive, cuts across all socioeconomic and ethnic lines, often escalates, and can be fatal. Research has shown that more than twice as many women are shot and killed by their partners than are murdered by strangers using guns, knives, or any other means. In fact, the risk of homicide in the home where a person has been previously hurt or hit in a family fight is 20 times greater if a gun is in the home than if it is not. Besides fatal and nonfatal trauma, violence against women increases health care use and cost and decreases the ability to follow treatment regimens. A law mandating the reporting of domestic violence has been passed in California, and similar laws are being considered in other states. All health professionals are in a key position to help battered women because the health care system serves as the point of entry for many of them, providing access to much-needed health, mental health, and related services.

The scope of the problem is substantial. Each year about 1.8 million women in the United States are beaten by current or former partners. Studies have shown that each year 14% to 25% of women using primary care clinics have been physically assaulted by their partners. The estimated prevalence of battering during pregnancy is between 7% and 17%. Among women presenting at an emergency department for injuries, about 20% have injuries related to domestic violence.

To detect domestic violence, awareness of its many presentations is helpful. Physical injury patterns associated with domestic violence generally involve contusions or minor lacerations to face, head, neck, chest, breast, abdomen, and perineum, although they may involve the extremities. Besides physical injuries, an increased prevalence of gastrointestinal disorders, pregnancy complications, sleep disorders, and chronic pain disorders is associated with domestic violence. The psychological symptoms associated with battering include fear, diminished self-esteem, symptoms of depression, suicide attempts, and a tendency to use and abuse alcohol and illegal drugs.

Despite the severe health implications of domestic violence, most physicians rarely ask about it. A lack of formal training, time constraints, and social biases such as gender stereotypes and the blaming of women all contribute to the barriers that prevent many clinicians from asking about domestic violence and making appropriate interventions.

Professional agencies have recently issued recommendations and guidelines to help health care professionals identify and treat battered women. These recommendations include asking about domestic violence as part of a general health screen with simple, direct questions in a nonjudgmental way and in a confidential setting. If domestic violence has occurred, the following recommendations apply:

- Listen to the patients' concerns about the abuse and review the dangerous health consequences with compassion and empathy;
- In addition to addressing the symptom(s) that precipitated the health care visit, assess psychological and physical health, such as alcohol abuse, and suicidal or homicidal tendencies;
- Ask about a battered woman's safety and the safety of any children in the home; make appropriate referrals such as providing written information (including phone numbers) on legal options, local counseling, crisis intervention services, shelters, and community resources;
- Create follow-up plans; and
- Specifically document symptoms, how injuries occurred, and the treatment plan, including steps taken to prevent further abuse.

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Responding to California's Tuberculosis Epidemic

MORE CASES OF TUBERCULOSIS are reported from California than from any other state. The 5,382 cases reported in 1992 represent a 54% increase since 1985. California's case rate of 17.2 per 100,000 exceeds the United States' case rate of 10.5 per 100,000, and is rising more sharply. Four California cities—San Francisco, Oakland, Santa Ana, and Los Angeles—are among the ten with the highest case rates of tuberculosis in the nation. California's Asians and Pacific Islanders, African Americans, and Latinos face tuberculosis rates that are, respectively, 11, 7, and 5 times higher than those in non-Latino whites. Of California's tuberculosis cases, 61% occur in persons born outside the United States. Because children younger than 5 years with tuberculosis have recently acquired their infections, the 37% rise in the case rate in this age group indicates ongoing transmission. The case rate in persons aged 25 to 44 years rose 39%, fueled at least in part by the related human immunodeficiency virus (HIV) epidemic.

To address the resurgence of tuberculosis, a broad-based public-private partnership developed and is implementing the *Strategic Plan for Tuberculosis Elimination and Control in California,* (published by the California Department of Health Services, Tuberculosis Control Branch, 1994).

Health care professionals are required to report a case or suspected case of tuberculosis to the local health department within seven days (title 17, California Code of Regulations, §2500 and §2505). Delays in identifying and reporting drug-resistant tuberculosis may have contributed to the prolonged infectiousness of an Orange

County high school student that led to at least ten secondary cases and scores of infections among classmates. The law now requires health care professionals' reports to include an individual treatment plan consisting of the name of the physician who has specifically agreed to provide medical care and other pertinent clinical or laboratory information required by the local health officer, such as drug susceptibility results (California Health and Safety Code, §3282). All persons from whom *Mycobacterium tuberculosis* is isolated should have drug susceptibility tests done on their first isolate, with results reported promptly to the local health department.

Physicians need to ensure that all patients with tuberculosis receive early and appropriate treatment and that it is completed. An estimated 590 patients (11%) with newly diagnosed tuberculosis in California in 1992 failed to complete appropriate therapy. These patients risk continued illness, contagion, and developing drug resistance. Health care professionals have a key role to play in keeping the frequency of multidrug-resistant tuberculosis (defined here as resistant to at least isoniazid and rifampin) at its presently estimated level in California of about 1%.

The initial treatment of tuberculosis should include four drugs—isoniazid, rifampin, pyrazinamide, and ethambutol hydrochloride or streptomycin—until drug susceptibility results are available, unless there is little possibility of drug resistance (for example, the community prevalence of isoniazid resistance is less than 4%). (In California, the estimated frequency of isoniazid resistance among newly diagnosed cases of tuberculosis is 11%.) When drug susceptibility results are available, the regimen should be altered as appropriate.

Directly observed therapy, where a responsible person observes while the patient ingests antituberculosis medicine, should be considered for all patients. Local health departments can assist in arranging daily or intermittent directly observed therapy, including providing such therapy in the field by culturally and linguistically competent outreach workers, and in referrals for needed services such as housing or drug treatment. Prescribing a combined preparation (Rifamate or Rifater, Marion Merrell Dow, Inc, Kansas City, Missouri) may help improve patient adherence and prevent resistance from developing.

To allow health departments to monitor the continuity of medical supervision, the law now requires that physicians keep written documentation of each patient's adherence to the individual treatment plan, and to report to the local health department any time a patient stops treatment (California Health and Safety Code, §3282). Before a patient with known or suspected tuberculosis is discharged from a hospital, the law now requires that the local health officer receive and approve the individual treatment plan (California Health and Safety Code, §3281). It also requires notification before a tuberculosis patient is released from any penal institution (California Health and Safety Code, §3281). Prompt identification, treatment, and isolation of patients with known or suspected tuberculosis remain urgent tasks for institutional infection control.

The law now also requires health care professionals to examine, or refer to a local health officer for examination, all household contacts of patients with tuberculosis (California Health and Safety Code, §3283). Because most children with tuberculosis acquired it from an infectious adult, prompt and thorough contact investigation of adult cases is essential. The rapid progression of tuberculosis in HIV-infected persons also necessitates increasing the tempo and completeness of contact investigations.

Information for health care professionals and multilingual patients is available from local health departments, local American Lung Association affiliates (1-800-LUNG-USA), or from the Tuberculosis Control Branch, California Department of Health Services, 2151 Berkeley Way, Room 715, Berkeley, CA 94704. Other states are also updating their tuberculosis control laws using the 1993 Centers for Disease Control and Prevention survey and recommendations.

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Injuries to Working Children

In the past decade injuries associated with child labor have reemerged as a public health problem. Once associated with poor working conditions in coal mines and southern textile mills, these injuries today reflect the increasing employment of children in service industries, agriculture, and construction. Child labor in the United States is defined by the Fair Labor Standards Act as the paid employment of persons younger than 18 years. The act prohibits children younger than 18 from 17 categories of work, including operating hazardous machinery, operating a motor vehicle in the course of work, operating construction equipment, and exposure to radioactive or toxic substances. In agriculture, however, workers 16 years of age and older are exempted from child labor laws. The number of children and adolescents in the United States who are legally employed exceeds 4 million, and 1 million children aged 14 and 15 work full- or part-time. The number of illegally employed children is unknown, but the US General Accounting Office found that the number of citations for illegal child employment has increased since the late 1980s. Injuries occurring during work done in violation of child labor laws are not "reportable," as the Fair Labor Standards Act is enforced by state labor departments, not health departments.

Data from the National Electronic Injury Surveillance System (NEISS) show that 16- and 17-year-old workers

have the second highest injury rates, exceeded only by 18- and 19-year-olds. Investigations by the US Occupational Safety and Health Administration (OSHA) reveal that each year about 100 children younger than 18 years are fatally injured at work and half of these are engaged in work activities prohibited by the Fair Labor Standards Act.

Morbidity data for work-related injuries are not available on a national basis by age, but New York State Workers' Compensation claims for 1980 to 1987 showed 9,656 work injuries in adolescents, and 43% of the claims were for permanent disability. Injury rates were lower in children than in adult workers, but the part-time nature of child and adolescent work makes comparison of rates difficult. Child workers may be less likely than adults to be covered by the Workers' Compensation system or to use the system to file a claim after an injury.

Children with work-related injuries present to physicians and to emergency departments in a manner similar to children in nonwork-related injuries. Although work injuries in children are not required to be reported by health care personnel, health care professionals can voluntarily report suspected violations of child labor laws to the Wage and Hour Division of their state department of labor. For example, a 16- or 17-year-old might be treated for injuries sustained in a motor vehicle crash while attempting to deliver pizza. The Fair Labor Standards Act prohibits such employment before age 18, regardless of the age at which a state issues a driver's license. These injuries and the name of the employer should be reported to the Wage and Hour Division for investigation. Except in the case of severe injuries, written referrals or complaints are more likely than telephone reports to result in investigations.

Work-related events are a substantial contributor to injury morbidity in older children and adolescents. Better data would help delineate this problem. Coordination between Wage and Hour inspectors, who enforce child labor laws, and OSHA would improve enforcement. Parents, teachers, and physicians should be aware of the hazards to working children.

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Prevention in Managed Care

ALTHOUGH MANAGED CARE ORGANIZATIONS seem to have unique advantages for providing superior prevention and early detection services, these advantages are rarely realized. This is difficult to understand because the required cost investments are dwarfed by those made routinely for new medical technologies and procedures.

A population-based perspective is the best way to provide prevention and early detection services. That is, service delivery should be designed to enhance the health of all of an organization's members. This may require structural changes in the organization, cultural and practice changes among the employees, developing user-friendly mechanisms for linking various databases, a process for ongoing evaluation, and committing resources necessary to start the process. There is evidence that patient cost-sharing reduces the use of necessary preventive services. To the extent that a managed care plan reduces or eliminates cost sharing for prevention, it can encourage the appropriate use of these services.

For example, consistent physician advice more than doubles the proportion of smokers who quit. Adding a brief nurse intervention after physician advice nearly doubles the effect of physician advice alone on long-term quit rates. The effectiveness of these interventions has been demonstrated; cost-effectiveness data show these practices to be more effective in saving years of life than most common medical practices. And yet, few medical care organizations integrate them into practice.

The benefits of increasing preventive services in other areas is less clear. For example, optimal breast and cervical cancer screening frequencies have been hotly debated. Guidelines have been developed and educational programs mounted to encourage screening at the appropriate times. But studies show that most cancers occur among persons who rarely, if ever, are screened; increasing the recommended screening frequency will not help such people, although it will dramatically increase costs. The cost of saving a year of life with cervical cancer screening at three-year intervals has been estimated at $120,000 and for screening at one-year intervals at well over $1 million. The cost-effectiveness of prevention depends on choosing the appropriate target population for the preventive service being offered.

Managed care organizations have the population base and the opportunity to link outpatient, inpatient, laboratory, and radiographic databases along with questionnaire data to develop low-cost automated systems that focus resources where they are most needed. For behavioral interventions such as smoking, models exist that add little, if any, time to an outpatient visit. But they require a structure for identifying the risk status, motivating and supporting intervention, and tracking progress (interest in and attempts at quitting). For screening studies, systems almost always exist for identifying persons in the base population who have not received a service for a specified interval beyond the optimal (often called a "safety net"). A systematic, automated outreach program can be used to encourage these persons to come in for the service. Because the safety-net interval is longer than the optimal interval, the costs of outreach are low and are limited to those persons at highest risk (such as those who rarely receive screening).

Finally, while preventive services delivered in the clinic are important, the major determinants of health and illness are lifestyle behaviors that can be addressed by community-based health promotion. Such community-

based approaches can enhance the effect of clinical preventive services.

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Routine Smoking Cessation Intervention in Health Care Systems

TOBACCO-RELATED ILLNESS and death is the largest public health epidemic of our times and, as such, warrants the application of population-based methods that have been the hallmark of successful public health programs. Whereas taxation, regulation, media reports, and other community approaches have been used to address this issue, smoking cessation interventions in health care systems, such as hospitals and outpatient clinics, should become an important component of the struggle against tobacco-induced disease. Medical system interventions have the potential to reach most smokers at a "teachable moment," without waiting for smokers to volunteer for more intensive group cessation intervention. (An estimated 70% of smokers visit a physician's office annually, and perhaps 25% or more receive inpatient services.)

Many research studies support the value of brief clinical interventions for tobacco use. These interventions include routine assessment of tobacco use in all patients, strong advice to quit, brief cessation counseling—including setting a quit date and prescribing pharmacologic aids as appropriate, state-of-the-art self-help materials, and follow-up support. These approaches produce long-term cessation in both outpatient and inpatient settings. Recent community-based data suggest, however, that smoking interventions that rely solely on physician initiatives are not systematically applied or sustainable in the real world of community practice. In fact, fewer than 50% of patients report they have ever been advised by their physicians to quit or cut down. Physicians often judge counseling interventions as important but relatively ineffective and outside their training. Smoking assessment and lifestyle counseling have not commonly been a part of medical education and practice; physicians striving to incorporate these practices face skill and habit barriers in addition to the obstacles posed by a work setting with time and resource limitations.

Incorporating systems for assessment, intervention, and follow-up into routine practice is a more effective method for improving smoking cessation success than simply relying on individual physicians and their willingness or ability to change practice patterns. Further, the most effective intervention systems are those that offer a range of options for quitting and involve physicians and nonphysicians alike. Smoking interventions provided by teams that include physicians and nonphysician clinical staff have recently been shown to be practical and acceptable in outpatient and inpatient settings. The use of nurses, health educators, respiratory therapists, and other available clinical staff to provide most intervention and follow-up elements minimizes the demands on physicians, spreads responsibility for the intervention across clinical staff, and increases the likelihood that the intervention will continue to be provided. Another method to encourage and sustain systematic smoking intervention in a medical setting is to identify it as a quality indicator.

According to recent estimates, more than 3 million smokers a year would quit if physicians could help only 10% of their smoking patients to quit. Because the tobacco industry successfully recruits about a million new smokers per year, the integration of systematic, low-intensity interventions throughout the medical care system could contribute substantially to achieving the nation's Healthy People 2000 smoking objectives.

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Vibrio vulnificus Hazard in Patients With Liver Disease

Vibrio cholerae has been long recognized as a human pathogen, but only in recent years has the pathogenicity of other Vibrionaceae been recognized. Eleven species of Vibrio are now known to be capable of causing serious human illness. Among these, *Vibrio vulnificus* is the most important in the United States.

Vibrio vulnificus is a naturally occurring marine bacterium found most often in warm ocean waters, such as the Gulf of Mexico. Humans may be exposed to the bacteria by swimming or wading in seawater or by eating raw seafood. Eating raw oysters is now recognized as the primary mode of acquiring *Vvulnificus* infection in the United States. Indeed, *Vvulnificus* has emerged as the leading cause of death from food-borne illness in some areas of the country.

In the 12-year period 1981 through 1992, 72 cases of *Vvulnificus* infection from eating raw oysters were reported in Florida; half of these persons died. These 36 deaths accounted for 80% of all food-borne deaths in Florida during this period. (Of note, eight of the nine other food-borne illness fatalities in Florida during these 12 years were due to infection with other *Vibrio* species.)

The case-fatality rate (63%) among patients with liver disease was nearly three times higher than for persons with normal livers. During 1991 and 1992, eight of nine persons dying of *Vvulnificus* infection after eating raw oysters in Florida had liver disease.

In California, where *Vibrio* infections were made a reportable condition in 1988, a similar relationship between *Vvulnificus* infection, raw oysters, and liver disease has been noted. From January 1983 through July 1993, 24 cases of *Vvulnificus* infection were reported to the California Department of Health Services; 18 of these persons (75%) died—almost all of primary septicemia. In 15 of the 24 patients (63%) there was a definite history of eating raw oysters before the onset of illness. In all cases where the source of the oysters could be determined, they were from the Gulf Coast. Of the 24 infected persons, 19 (80%) had an underlying chronic illness; in 16 of them (85%) the condition was alcoholic cirrhosis or other liver disease.

The risk of infection after ingesting raw oysters harboring *Vvulnificus* in persons having underlying liver disease is 30 times greater than in normally healthy persons, and the risk of death is more than 200 times greater. Even with the advanced medical treatment, persons having liver disease have a 50% to 60% case-fatality rate in the event of *Vvulnificus* septicemia.

Because *Vvulnificus* is a naturally occurring bacterium whose presence is not due to sewage or other contamination, there are no sanitation or other public health controls that can limit the harvesting of oysters to only areas free of the pathogen. For this reason, California enacted regulations in 1990 requiring restaurants and other establishments that serve or sell Gulf Coast oysters to warn prospective purchasers about possible ill effects. (The regulations also specify requirements for tagging, labeling, and records retention to facilitate prompt identification of the source in the event of illness.) More recently both Florida and Louisiana have enacted similar regulations, and some other states are considering taking action as well.

Although a growing number of areas require a public warning about the potential of raw oysters to cause serious illness in immunocompromised persons, clinicians must advise their patients with liver disease of the potential for illness and death from *Vvulnificus* infection secondary to eating raw oysters, even though the oysters have been legally harvested and properly handled. Indeed, persons with liver disease should be strongly advised not to eat any seafood that has not been thoroughly cooked. Likewise, persons having liver disease or who are immunocompromised from other causes should be advised that serious and possibly fatal *Vvulnificus* soft tissue infection may result from marine trauma or when open wounds are exposed to seawater. Marine-acquired wounds in immunocompromised persons must be closely observed, and even minor wounds may warrant antibiotic treatment with oral tetracycline, the combination product trimethoprim and sulfamethoxazole, or a quinolone.

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Alerts, Notices, and Case Reports

Pulmonary Alveolar Lipoproteinosis

Remission After Antibiotic Treatment

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PULMONARY ALVEOLAR LIPOPROTEINOSIS is an unusual cause of airspace consolidation that frequently requires invasive procedures for treatment.[1] There are two types of this disorder: an idiopathic primary type, and a secondary type that occurs in response to various conditions including inhalant dusts and mycobacterial and cytomegaloviral infections.[2,3] We report a case of an elderly immunocompetent patient who was diagnosed with pulmonary alveolar proteinosis associated with anaerobic lung infection and whose response to antibiotic therapy and subsequent relapse suggest a cause-and-effect relationship.

Report of a Case

The patient, an 80-year-old man who had been in excellent health, was referred for evaluation because of a gradual onset of exertional dyspnea and nonproductive cough. These symptoms presented over several months and were accompanied by a 3.6-kg (8-lb) weight loss, night sweats, and increasing fatigue. A chest radiograph (Figure 1) and computed tomography showed patchy alveolar infiltrates in the right upper, right middle, and left lower lobes.

The patient's medical history was relevant for mildly symptomatic benign prostatic hypertrophy and quiescent peptic ulcer disease. He had an incidental splenectomy in 1967 after a cholecystectomy. He had been a moderate tobacco smoker of 25 pack-years but had stopped in 1978. He had no history of drug abuse, homosexual contacts, or previous blood product transfusions. He had no history of malignancy or exposure to silica dusts.

On examination the patient was thin and afebrile with obvious muscle wasting. Examination of the chest was remarkable for fine inspiratory crackles in the left lung base and right mid-lung field. There was no hepatomegaly, adenopathy, or clubbing.

A complete blood count showed a leukocyte count of 9.4×10^9 per liter (9,400 cells per mm^3) and a hemoglobin level of 124 grams per liter (12.4 grams per dl). A Westergren erythrocyte sedimentation rate was elevated at 89 mm per hour. The results of hepatic and renal studies were normal. Skin tests including a 5-tuberculin-unit purified protein-derivative and 1:100 coccidioidin were negative, and serologic tests for coccidioidomycosis, histoplasmosis, and cryptococcosis were negative. Human immunodeficiency virus testing was negative. Gram's and acid-fast stains of sputum were negative. Multiple sputum cultures were negative for mycobacteria or fungi. Pulmonary function tests, including the measurement of carbon monoxide diffusing capacity, were normal when the results were adjusted for age. Arterial blood gas measurements with the patient breathing room air showed a pH of 7.40, a P_{O_2} of 68 mm of mercury, and a P_{CO_2} of 38 mm of mercury.

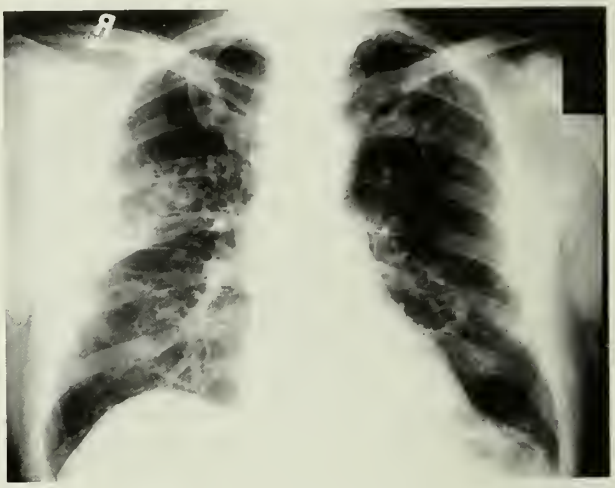

Figure 1.—The initial chest radiograph shows patchy infiltrates.

Flexible fiberoptic bronchoscopy disclosed a normal tracheobronchial tree. A 100-ml bronchoalveolar lavage returned copious amounts of a tan, viscous fluid. Transbronchial lung biopsies from the anterior segment of the right upper lobe showed all alveolar spaces filled by a granular periodic acid-Schiff (PAS)-positive, diastase-resistant material with occasional foamy macrophages (Figures 2 and 3). A mucicarmine stain of the lung specimen was negative, and there was mild hyperplasia of the type 2 pneumocytes. Special stains were negative for organisms. The pathologic diagnosis was pulmonary alveolar proteinosis. Bronchoalveolar lavage fluid had a luxuriant growth of γ-streptococcus on anaerobic culture.

A thorough evaluation showed no underlying malignancy or immunodeficiency. A barium swallow study failed to show evidence of a swallowing dysfunction or gastroesophageal reflux. A regimen of clindamycin, 300 mg orally three times a day, was started. He achieved remarkable relief of his symptoms after two weeks of therapy. His radiographic infiltrates cleared after eight weeks of therapy, and he stopped losing weight.

(Gumpert BC, Nowacki MR, Amundson DE: Pulmonary alveolar lipoproteinosis—Remission after antibiotic treatment. West J Med 1994; 161:66-68)

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Figure 2.—Pulmonary alveolar lipoproteinosis with diastase (magnification × 100) shows alveoli distended with granular diastase-resistant material.

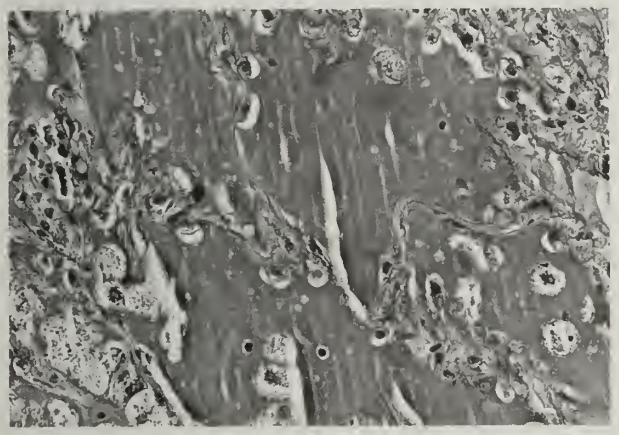

Figure 3.—Pulmonary alveolar lipoproteinosis (PAS) with diastase (magnification × 400) shows alveoli that are completely distended with PAS-positive material, along with the presence of foamy alveolar macrophages.

The patient returned ten months later with a recurrence of chronic, nonproductive cough, malaise, and dyspnea. Chest radiographs again showed bilateral patchy infiltrates in the right upper and left lower lobes. The initial examination, laboratory tests, and sputum evaluations were unrevealing. A bronchoscopy again showed normal airways and returned a viscous tan effluent on lavage. Special stains of the lavage showed it to be PAS-positive, diastase-resistant, and metachromatic with toluidine blue. A protected specimen brush of the right upper lobe anterior segment grew the same anaerobic streptococcus. A six-week course of clindamycin and ciprofloxacin resulted in the return of the patient's constitutional well-being and clearing of the pulmonary infiltrates. A regimen of a daily suppressive dose of clindamycin was maintained for a year without evidence of recurrence.

Discussion

Prakash and associates recently summarized their retrospective experience with pulmonary alveolar lipoproteinosis.[1] Of the 34 cases they reviewed, 5 were thought to represent the secondary type, and these cases were in patients with hematologic malignant disorders. Clinically, all patients presented with cough and dyspnea, and the two types of pulmonary lipoproteinosis could not be distinguished. Although the classic chest radiograph in this disorder shows hazy perihilar infiltrates, 18% of the Mayo Clinic cases showed asymmetric, bilateral, patchy peripheral infiltrates. Sputum specimens were positive in three of these cases. One patient had *Mycobacterium intracellulare*, one grew a *Pseudomonas* species, and *Pneumocystis carinii* was found in the third case. Most of their patients were successfully treated with whole lung lavage, but there was a 15% recurrence rate during the following five-year period.

Our patient had a clinical presentation and lung disease consistent with the diagnosis of pulmonary alveolar lipoproteinosis that was associated with culture evidence of an anaerobic lung infection. All symptoms and signs of this disorder responded to antibiotic therapy. We were unable to find a predisposing condition or malignant lesion after two years of follow-up, and we report this case because of its uniqueness. It is possible that our patient has intermittent pulmonary aspiration, but he has been without recurrence while on long-term antibiotic therapy alone.

Lung infections in association with pulmonary alveolar lipoproteinosis have been noted in several reviews; however, most of these infections have been thought to be superinfections.[4,5] *Mycobacterium tuberculosis* has been reported to cause a similar reaction,[3,6] and the condition resolved with antituberculous therapy. More recently, both primary and secondary pulmonary alveolar proteinosis have been described in patients with the acquired immunodeficiency syndrome, most commonly in association with *P carinii* infection.

Conclusion

Our report of an immunocompetent elderly man in whom a lung reaction resembling pulmonary alveolar lipoproteinosis developed to an anaerobic lung infection is unique. Twice he responded to conservative antibiotic therapy. Our case shows that the lung can respond in a variety of ways to several inciting events. This disorder is one type of idiosyncratic reaction that may be caused by a wide variety of stimuli. In evaluating a patient with pulmonary alveolar proteinosis, infectious causes should be aggressively investigated and treated. Chronic anaerobic lung infections should be added to the list of causes of alveolar proteinosis.

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Methomyl-Induced Carbamate Poisoning Treated With Pralidoxime Chloride

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METHOMYL is a carbamate insecticide marketed under the trade names Lannate and Nudrin.[1(pC199)] Similar to organophosphate pesticides, methomyl inhibits acetylcholinesterase (AChE) activity in the peripheral nervous system and disrupts normal nerve synaptic function.[2,3] Differentiating carbamates from organophosphates based on clinical presentation is often difficult because of the similarity of symptoms,[4] yet urgent treatment decisions must often precede analytical or historical confirmation. Atropine is the primary drug used to treat symptomatic cases involving both organophosphate and carbamate insecticides. The use of pralidoxime chloride is recommended, along with atropine, for nicotinic symptoms of organophosphate poisoning, but the recommendations to use pralidoxime in patients with similar symptoms caused by a carbamate insecticide are much less clear.

We review data regarding pralidoxime chloride and carbamate poisonings and present a case of an accidental ingestion of an unknown pesticide in a middle-aged man who had classic muscarinic and nicotinic symptoms consistent with an organophosphate insecticide exposure. Treatment with intravenous atropine was partially successful, but prominent nicotinic symptoms suggested the need for pralidoxime chloride. This was noticeably effective and immediately reversed the nicotinic toxicity. We hope to clarify the usefulness and safety of pralidoxime in cases of carbamate poisoning.

Report of a Case

The patient, a 52-year-old man weighing an estimated 60 kg (132 lb), accidentally ingested "one gulp" of a chemical with the color and general appearance of a cola drink that had been stored in a 2-liter Pepsi bottle. After the drink, he lay down for nearly half an hour before becoming ill, but he had no emesis. On presenting to the emergency department about 45 minutes after drinking the liquid, the patient was stuporous (Glasgow Coma Scale of 11) and in acute respiratory distress. His temperature was 37.1°C, pulse 146 beats per minute and regular, blood pressure 228/120 mm of mercury, and respirations 44 per minute. His skin was wet and smelled of camphor. No solvent or pesticide-like odor was noted. His pupils were 1 mm in diameter, and pink, frothy secretions were present in the oropharynx. Auscultation revealed wet-sounding inspiratory and expiratory rales and rhonchi plus expiratory wheezes. His heart rhythm was regular and rapid with no murmur or gallop. The abdomen was soft with active bowel sounds. The patient was noted to be incontinent of stool. Coarse muscle fasciculations were noted in his extremities.

The patient had poured the suspected liquid over ice before drinking it. Poison Control Center staff examining the specimen for color and odor concluded that it had a distinctive odor, but could not identify it; neither could a licensed pest-control adviser who regularly uses pesticides in the San Joaquin Valley of California. On the basis of the history of possible herbicide ingestion, a "shake and bake" test to rule out paraquat or diquat was done and proved negative. A positive test would show an intense blue-green color.[5] From the clinical presentation, the substance was thought to be an organophosphate insecticide.

Emergency department treatment included nasotracheal intubation, which produced projectile, pink, frothy secretions as the tube entered the trachea, and mechanical ventilation. Atropine sulfate, 6 mg, was administered intravenously in the first ten minutes, which cleared the lungs and dropped the heart rate from 146 to 111 beats per minute. Pralidoxime, 1 gram, was administered intravenously five minutes after the last dose of atropine. Fasciculations were not noted to stop after the atropine was given, but did after the patient received pralidoxime, only to resume 30 minutes later. A second dose of pralidoxime, 1 gram given intravenously, again clearly stopped the fasciculations.

A regimen of atropine, 3 mg per hour, and pralidoxime, 500 mg per hour, was begun as continuous infusions. Gastrointestinal decontamination was carried out using a large-bore orogastric tube. Aqueous activated charcoal, 100 grams, was instilled into the tube followed by gastric lavage until clear, followed by 100 grams of aqueous activated charcoal. The tube was then removed.

Laboratory results showed an initial—specimen drawn immediately before the first dose of pralidoxime—erythrocyte cholinesterase level of 8 mmol per ml per minute (normal, 9 to 18) and a plasma cholinesterase level of 3 mmol per ml per minute (normal, 7 to 19).

After the administration of atropine and pralidoxime, rapid and pronounced clinical improvement occurred. Within an hour the patient's lungs were clear to auscultation and he nodded yes or no appropriately to questions. By three hours, he was able to write appropriate answers to questions. The patient was agitated, however, and required physical restraints and sedation with benzodi-

(Ekins BR, Geller RJ: Methomyl-induced carbamate poisoning treated with pralidoxime chloride. West J Med 1994; 161:68-70)

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azepines. The atropine infusion was discontinued four hours after presentation because a clinical end point of clear, dry lungs had been reached. No more was administered. Pralidoxime therapy was discontinued after 28 hours. A total of 18 mg of atropine (6 mg in the emergency department and 3 mg per hour for 4 hours) and 16 grams of pralidoxime (2 grams in the emergency department and 0.5 mg per hour for 28 hours) was given.

The endotracheal tube was removed after 44 hours, but the patient still had a substantial degree of agitation. Neither hypoxemia nor hypoglycemia was present. After 48 hours his neurologic status improved markedly. He remained in the hospital for nine days because of pneumonia caused by *Haemophilus influenzae*.

Methods

An aliquot of the suspected pesticide was sent to the California Department of Food and Agriculture, Fresno.* Using acetone as the solvent, the specimen was injected into a Hewlett-Packard 5890 gas chromatograph connected to a Hewlett-Packard 5970B mass spectrometer. The resultant spectra from the mass spectrometer suggested methomyl. A known standard of methomyl was injected into the gas chromatograph-mass spectrometer using the same indicators to make a positive identification. A separate aliquot of the suspected pesticide was dissolved in methanol and subjected to quantitative analysis using high-pressure liquid chromatography, which confirmed it to be methomyl. Because of the desire to corroborate the identity of the pesticide and to rule out any contaminant, the manufacturer of Lannate (methomyl), DuPont Agricultural Products, was asked to analyze the unknown liquid. The company's chemists noted that the specimen provided had the odor and appearance of Lannate L. It was analyzed by liquid chromatography and mass spectrometry. After dilution in distilled water, it was injected into a packed liquid chromatography column interfaced to a Finnigan MAT Model 900 mass spectrometer with a continuous-flow fast atom bombardment interface. An Iso Model CV4 UV detector was connected in-line between the liquid chromatography column and mass spectrometer and was set at 239-nm wavelengths. The specimen was found to contain methomyl in the same proportion as Lannate L (25%). There was no evidence of other chemicals. Cholinesterase determinations were done using the ΔpH (Michel) method.[6]

Discussion

Methomyl is a highly toxic methyl carbamate pesticide of restricted use, available only to approved and licensed applicators in the United States.[1,7-10] In our experience, this unfortunately does not limit poisonings solely to occupational settings.

Methomyl produces classic cholinergic symptoms,[3] including nausea, vomiting, sweating, salivation, lacrimation, urination, defecation, miosis, excitation, ataxia, muscular spasm and weakness, difficult or labored breathing, and in severe cases, seizures and death.[8-10] Cases of methomyl poisoning have been reported in many settings: agriculture, food contamination, deliberate ingestions, and accidental and occupational intoxications. All standard information sources examined suggest that the clinical approach to carbamate intoxication is similar to that to organophosphates, except with regard to the use of pralidoxime chloride, which is generally discouraged. Atropine is always the primary pharmacologic intervention recommended for muscarinic symptoms from either carbamates or organophosphates.

The mechanistic similarities between organophosphate and carbamate insecticides are that both produce acetylcholinesterase inhibition. The manifestation of AChE excess is one of a cholinergic crisis. The difference between organophosphates and carbamates is that organophosphates produce a permanent inhibition of the AChE enzyme whereas the carbamate-AChE bond is reversible, producing a shorter intoxication and ultimately a less ominous case of poisoning.

The use of pralidoxime in carbamate intoxications is often not recommended, is considered unnecessary, or is specifically contraindicated, especially with the use of carbaryl (Sevin). Many authors, including some who suggested its contraindication, agree that in unknown or mixed cholinesterase-inhibitor intoxications, pralidoxime therapy should be given. In part, because of these standard recommendations, pralidoxime is not routinely used in carbamate intoxications. Besides the aforementioned favorable experience, however, there are other reports of benefit from pralidoxime use in patients with exposure to carbamate. A seriously ill patient survived after 40 hours of treatment with both atropine and pralidoxime. Therapy was based on the presence of prominent cholinergic symptoms. Later it was determined that he had had exposure to aldicarb (Temik), a carbamate pesticide.[11] Another case involved a 16-month-old infant thought to have eaten rat poison. She was treated with atropine and pralidoxime because of the clinical presentation. She was extubated soon after receiving 250 mg of pralidoxime for nicotinic symptoms and recovered uneventfully.[12]

Pralidoxime chloride should counteract the nicotinic effects—paralysis of respiratory skeletal muscles, fasciculations—associated with carbamate pesticide toxicity.[11]

The following reasons are cited for hesitating to treat carbamate exposures with pralidoxime:

- Autoreversibility of the carbamate AChE-bond,[4,13]
- The short duration of binding between the carbamate moiety and AChE,
- Based on accepted mechanisms of action, there is no rationale for pralidoxime to be effective,[14] or
- Pralidoxime increases the toxicity of an exposure to carbamates.[15-18]

Consistency and rationale fail to follow logic if on the one hand pralidoxime is dangerous to give if the toxin is known to be a carbamate, but it is acceptable to administer if the pesticide involved is unknown or if it is a mixed

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intoxication with organophosphates. Studies in animals that suggest toxicity associated with the use of pralidoxime in carbamate poisonings have been criticized on methodologic grounds and for the small number of animals used.[19] Further, the studies were done using different oximes or salt forms of pralidoxime not found in this country.[15-18]

The adverse effects profile of pralidoxime has been reviewed and noted to be relatively free of any serious side effects.[20,21] At doses of 15 to 30 mg per kg of pralidoxime iodide, no important changes in blood pressure, electrocardiographic, or respiratory patterns were reported.[22] Others have noted no adverse symptoms of pralidoxime iodide at 15 to 30 mg per kg in adults, but at doses of 45 mg per kg, pronounced hypertension (diastolic blood pressure >110 mm of mercury) and electrocardiographic changes (T wave amplitude and PR interval prolongation) developed.[23] In both reports, the authors used the iodine salt form, which is no longer used and was associated with a host of other minor effects such as blurred vision, dizziness, diplopia, headache, and a bitter taste.[22,23] The use of pralidoxime chloride has not been associated with reports of hypertension or electrocardiographic changes. The risk of introducing a serious adverse reaction from pralidoxime chloride appears extremely low.

Carbamylation of the AChE enzyme is reported to be short-lived.[3] Carbamates are reported to hydrolyze spontaneously from the cholinesterase enzymatic site within 48 hours.[24] It is suggested that enzyme activity may be restored rapidly—often within minutes—as a result of spontaneous hydrolysis of the carbamate-AChE complex. It was reported in 1977 that AChE levels return to normal within 48 hours and that the analytical method used may also affect the in vitro regeneration.[25] Although it is not clear if oximes can decarbamylate AChE enzymes, similar to that which occurs with organophosphates, several possible therapeutic effects by oximes have been cited[17]: a cholinesterase-stimulating property, parasympathetic receptor blocking effect, neuromuscular blocking action, or a direct effect on the receptivity of nicotinic receptors in sympathetic ganglia.

If the spontaneous return to normal occurs rapidly (but not until 48 hours) and if the use of pralidoxime hastens recovery in the first 24 to 48 hours, logically the addition of an oxime during the early stages of treatment would be beneficial. Pralidoxime may regenerate AChE, making it crucial to draw blood specimens for erythrocyte and plasma cholinesterase levels before pralidoxime is administered. For much the same reason, serial AChE levels after giving pralidoxime are not helpful.

In this patient, a rapid reversal of muscle fasciculation was demonstrated twice after the administration of 1 gram of pralidoxime per dose with a continuous infusion for 28 hours. This description is consistent with a drug effect and not spontaneous reversal.

Pralidoxime chloride is not expected to correct muscarinic toxicity directly. By regenerating AChE, it becomes "atropine sparing," thus contributing to the amelioration seen. Although it is widely held that pralidoxime cannot penetrate the central nervous system or correct central nervous system toxicity of AChE inhibitors, a well-substantiated human case with both clinical findings and electroencephalographic recordings suggests otherwise.[26] A 3½-year-old child poisoned with parathion regained consciousness and had a dramatic correction in the electroencephalogram within two minutes after receiving a 500-mg dose of pralidoxime.

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Special Series

Future of Health Care Reform
The Effects on Physicians

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The scope, timing, and effects of the health care reforms that many informed persons advocate cannot be specified in detail because before they become operational they must still be negotiated in three different arenas—Congress, state legislatures, and the marketplace. Because the introduction of major reforms will affect the operations of the extant health care system, additional reforms will be required, the nature and extent of which cannot be predicted until initial reforms have been implemented and the results examined. Because of this series of chain reactions, any serious effort to sketch the future of health care reforms and, more particularly, to focus on how they are likely to affect physicians, must be more speculative than definitive.

Despite these inherent difficulties, some clarifications can be made by identifying four major areas where reforms are likely to be introduced in the near or mid-term:

- Providing the entire citizenry with health insurance coverage,
- Moderating the additional dollars flowing into the health care sector,
- Changing the organization and delivery of health care services, and
- Constraining capital investments.

Other targets for early reform can be identified, but any listing would overlap, to a greater or lesser degree, these areas. The more important challenge is to explore how the reforms within these areas are likely to affect our present health care system and, more particularly, how physicians are likely to practice in the future.

Universal Coverage

President Clinton has emphasized not once but many times since his September 1993 address to Congress on health care reform that he is open to all sorts of negotiations with Congress about the specifics of the legislative program that they will develop and pass as long as universal coverage is included. When one recognizes that this country spends about 40% more per capita than the next-highest spending nations for health care and that the other advanced countries have provided coverage for many years to their entire population, the time is long overdue for the United States to take action on universal coverage.

Such action will increase the demand for physician services and thereby have a favorable effect on the earnings of the medical profession. There is a second reason to view universal coverage as a boost to physicians: they will no longer have to explain to themselves, the public, and the uninsured why they avoid treating indigent patients.

The President's proposal for universal coverage is linked to a specified package of essential services that is modeled after the health benefits currently provided by Fortune 500 companies. Although this is a good package of benefits, the planned coverage will be less extensive than that now enjoyed by a minority of those with full coverage.

One of the striking features of our health care system has been the proclivity of the medical profession to undertake any and all diagnostic and therapeutic procedures that appear to hold promise for their patients without concern for the cost/benefit of successive medical interventions. In the new era of severe dollar constraints, the perpetuation of such an open-ended patient care strategy will not be sustainable. Physicians have protested repeatedly about the growing constraints on their clinical freedom, but the odds favor a still more contentious environment if universal coverage brings with it, as it must, a specification of the services that the system will and will not pay for.

A related observation: although informal rationing has always been part and parcel of the health care system in the United States, the criteria used to decide who will have access to more costly procedures such as a heart or liver transplant have usually been obscured. But well-to-do patients have always enjoyed preferred access. In the face of universal coverage with accompanying dollar constraints, the American people will be under increasing pressure to confront the implications of overt rather than sub rosa rationing. Such a challenge will require the active participation of physicians, who are in the best posi-

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tion to assess the therapeutic benefits of costly and risky procedures. But decisions affecting the allocation of scarce medical resources in a democracy can never be left solely to the medical profession.

Moderating the Flow of New Dollars Into the System

The urgency for slowing dollar expenditures increases. The United States cannot much longer tolerate adding new funds for health care at a rate two to three times as fast as the growth of its gross domestic product. The trillion-dollar level for health care outlays will be breached in 1994, and current projections point to a 2-trillion dollar figure by 2000 or shortly thereafter. The dollar flow into the health care sector must be slowed. We are, however, still far from an agreement about how this objective is to be achieved. President Clinton has recommended that Congress cut back substantially on future appropriations for Medicare and also increase the copayments of the more affluent elderly for Medicare B premiums. Others look to reducing or eliminating federal subsidies for health insurance, which total over $70 billion a year, to help constrain consumer demand. Still others advocate an intensified reliance on competitive forces by building up strong regional health alliances that would be able to bargain more effectively with physicians and hospitals.

What are the likely consequences of a reduced rate of dollar inflow into the health care system? First, fewer total health care dollars will mean fewer dollars to compensate the ever-increasing supply of practicing physicians. Inadequate attention has been paid to the fact that between 1960 and today, the physician supply per 100,000 has increased from 140 to 250, an increase of almost 80%. Despite this, physician earnings have substantially outpaced the increase in earnings of a typical worker. The earnings of physicians in 1992 after expenses but before taxes averaged $164,000. This paradoxical increase between the growth in the number of physicians at the same time that their earnings increased was possible only because of the large amounts of new money entering the health care system. In 1965, on the eve of the implementation of Medicare and Medicaid, total national health care expenditure in constant dollars was approximately $150 billion. By the end of 1994, there will have been more than a sixfold increase to $1 trillion.

Any serious effort to slow the flow of total dollars into the health care system is likely to force individuals and families to cover a higher proportion of total expenditures through out-of-pocket payments, which is likely to have a moderating effect on physicians' earnings.

The more dollar-constrained the health care system becomes, the more likely it is that in a reduced demand for physician services, greater reliance on mid-level health personnel, and added payer resistance to physician fee increases will result, foreshadowed by the recently enacted resource-based relative-value-scale reimbursement approach introduced by Medicare.

Some counterforces are likely to lead to an increased demand for physician services if and when universal coverage is implemented, but it is unlikely that even in the face of an expanded total demand for health care services, physicians' earnings will continue to increase at the same rate as in the past. The more likely outcome is a retardation in the rate of growth of physicians' earnings.

Organization and Delivery Reforms

There is growing recognition that the private health insurance industry has contributed to the large number of persons without insurance and the unease experienced by a still larger number that they may lose their insurance coverage if they change jobs. The Health Insurance Association of America, cognizant of the growing criticisms levied against the industry and traumatized by the recent resignation of several of its largest members, proposed at the end of 1992 that it would cooperate with the federal government to assure universal coverage. This action represents a reversal of the 40-year strategy during which the private insurance companies splintered the insurance pool to improve their profitability by pursuing risk management tactics directed at identifying and covering only the best risks.

Reacting to the growing trend of employers to self-insure—about 60% of all employees are in employer self-insured plans—such large insurance companies as Cigna, Aetna, Metropolitan, and Prudential have developed managed care networks, through shared-risk contracts with large employers in which they identify preferred physicians and hospitals that offer quality health care at a competitive price. A correlate of such risk contracts is the willingness of physicians and hospitals to participate in accountability systems that such risk contracting requires.

Another consequence of these managed care arrangements is the changes introduced in the reimbursement patterns for physician services. In the place of fee-for-service, physicians who join such networks may accept capitation, go on salary, or agree to still other modes of reimbursement that differ substantially from fee-for-service.

A likely concomitant of the changes under way in the organization and delivery of health care, especially in an era of reduced rates of total dollar outlays, will be the rapid decline in the number of physicians who practice solo or in small groups. These practice arrangements, though having many advantages, also have high costs and limited market power. Larger group practices hold the promise of substantial savings in support personnel, medical equipment, rent, and other office expenditures.

Capital Investments

The fourth major area in which longer-range reforms are likely to be initiated in the near and middle term relates to capital investments. These affect the number and types of physicians trained; the size of the hospital plant, equipment, and personnel staffing ratios; and the trends for biomedical research and development, by both the federal government and industry.

The expansion of the physician supply in the 1960s

and 1970s was undertaken with little attention to the costs of enlarging the educational infrastructure and even less to the substantial financial consequences for the health care system. Had we increased over the past three decades the total supply of physicians by 40% instead of 80%, our 1994 outlays for medical care might have been $300 billion lower.

Currently the American Medical Assocation, the American Association of Medical Colleges, the Committee on Graduate Medical Education, the Physician Payment Review Commission, and still other governmental and advisory bodies are sending the same signals: contain the future supply of physicians, decrease the relative number of specialists, and pay more attention to linking physicians to underserved populations.

With an increasing number of students graduating from medical school with an average debt of $70,000 or higher, it should not prove difficult for the federal government alone or in association with the states to put effective arrangements in place whereby the debts of young physicians are canceled for several years of service among underserved rural and inner-city groups.

The federal government is also likely to take early action to modify the conditions governing graduate medical education funding so that more support is provided for residency training for generalists rather than for specialists. The more difficult challenge will be for states, particularly those with several medical schools, to merge or close their smaller and less effective schools.

In the short span between 1985 and 1992, national support for health research and development increased from $13.6 billion to $28.1 billion, with industry's share growing so rapidly that it overtook the federal government's contribution of $11.6 billion.

We must assume that if major reforms to constrain future health care spending are introduced and implemented in the near and middle term, such efforts will inevitably be reflected in some moderation of new investments in research and development. The likely effect on development is the focus of the industry's concern. Hospitals facing tightened budgets will move more slowly to purchase the latest (and more expensive) pieces of equipment. In turn, the medical supply companies are likely to moderate their research and development expenditures.

But there are additional forces at work that are likely to slow the purchases of expensive new equipment. Medicare has taken some selective actions both to resort to technology assessment before authorizing reimbursement and to restrict expensive procedures such as heart transplants to a limited number of medical centers.

A more controlled and constrained financial health care environment will underpin the continuing shift of treatment to ambulatory care settings that will be reflected sooner or later in a notable decline in the number of acute care hospitals. The combination of constrained dollars and fewer inpatients points to a substantial shrinkage in hospital capacity in the decade ahead. Such a shrinkage will have an important effect on patients' access to care and on the future earnings of physicians. The closing of a local hospital is often a prelude to the relocation of physicians or to difficulties in recruiting physicians to replace those who retire or die.

A Look to the Future

Brief attention should be directed to a few of the more important consequences of health care reform on the future shape and functioning of the US health care system, with particular attention on how the reforms are likely to affect physicians.

An increasing proportion of all patients are likely to become members of large insured groups that will enter into long-term relations with designated physicians and hospitals. Enrollees will be under strong financial and other pressures to seek treatment from designated providers whose payments will depend little, if at all, on a fee-for-service arrangement. If this is the wave of the future, physicians will find it necessary to join such large group arrangements where they will probably have considerably less clinical and economic freedom than they presently enjoy under a solo or small group practice based on fee-for-service. The fact remains that the best—perhaps the only—prospect of constraining the total costs of US health care involves substantial alterations in how physicians currently practice, how they are paid, and how much they are permitted to earn.

Clearly such reforms affecting the financing and delivery of health care services as have been outlined here will also have important effects on patients' choices and their satisfaction with the medical care they receive. The scale and scope of the choices available to them as to their principal physician and the specialists they may want or need to consult will be largely determined by the health care plan to which they belong. Those with more disposable income, particularly the wealthy, will probably encounter little difficulty in maintaining the high degree of freedom of choice that they now enjoy in selecting physicians and in securing expensive modes of treatment.

In 1974 the United States resorted to federal and state governmental planning in order to control capital investments in hospitals and costly equipment, but the legislation was permitted to lapse after a few years because of the cumbersome machinery needed to implement "certificates of need." The fact that the nation dropped the regulation of capital investments in the past does not preclude a second and broader attempt in the future to place a lid on total health care outlays (global budgeting), an objective that will also necessitate controlling capital investments.

It is almost certain that decision making regarding the number, types, and deployment of physicians in the future will see enlarged roles for both the federal and state governments. Neither universal coverage nor cost controls can be achieved without more effective planning and deployment of health care personnel, particularly physicians, who are and will continue to be key to the delivery of effective health care services to the American people.

Special Series

Rationing—Missing Ingredient in Health Care Reform

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A patient in a cardiac intensive care unit used 750 units of blood in the five days between his surgical procedure and his death. His initial surgical procedure lasted 17 hours because of profuse bleeding. After two hours in the intensive care unit, he was taken back into the operating room for another five hours. When he again came to the intensive care unit, his surgeons were still unable to staunch his bleeding, yet continued to order infusions of blood.

* * *

A patient has again gone into liver failure after receiving a second transplanted liver; now only a third liver transplantation can save her life. No one knows why the two previous transplants failed. She does not have hepatitis B, which would automatically disqualify her from liver transplantation, but she does have symptoms similar to those expected with hepatitis B. Ought she to receive a third liver transplant?

* * *

A 26-year-old woman, a Medicaid patient who had been on hemodialysis for end-stage renal disease since 1989, had a cardiopulmonary arrest. The resuscitation attempt lasted for more than 45 minutes. By the time her heart was beating again, she had extensive, permanent, and irreversible brain damage. Neurologic tests subsequently determined her to be neocortically dead, and she was pronounced to be in a persistent vegetative state. Nevertheless, her family insists on continued hemodialysis and threatens to sue her physicians and the hospital if the family's demands are not met. A year later, she is still receiving hemodialysis three times a week.

Although American medicine is in many ways the finest in the world, from an ethical perspective our health care system (or nonsystem) has been subject to legitimate criticism on three counts: cost, unequal access, and uneven quality.

We have dodged these issues for decades, but there are now several proposals for reform. How adequately do they respond to these ethical concerns about cost, access, and quality?

Providing universal access to medical care is the right thing to do, not merely from an ethical perspective, but also from the standpoint of economics. If the uninsured, the uninsurable, and the underinsured have had no direct access to the system, they have had indirect access to it after they have become so sick as to require treatment on an emergency basis. Emergency department care is costlier than routine, timely, proactive, preventive, and health maintenance services.[1] The burden of meeting these higher costs has fallen on society as a whole, contributing to spiraling inflation in the health care sector. For insisting that health care reform include universal coverage and that it provide all citizens with the security of knowing that their health care benefits cannot be lost, no matter what may happen to their jobs, the Clinton Administration is to be commended.

I am skeptical that any of the plans can effectively hold down costs, for one important reason: all the proposals fail to admit the need for rationing. If national health care expenditures are to be held rigidly within a global budget, and if every American is to be afforded health care benefits, then we cannot all have everything we want in the way of medical services. Within a finite budget, it is impossible to satisfy both objectives of utilitarianism—providing the greatest good for the greatest number. If the emphasis is to be on the greatest number, the "good" to be offered necessarily must be limited. Conversely, if the emphasis is on providing the greatest possible "good," then the number of those eligible to receive what is provided will have to be reduced.

Theoretically, "utility" or "the good" is not precisely defined. In practice, the theoretical notion of utility translates into tangible goods and services. Medical care is among these.

The state of Oregon squarely faced up to this. The aim was to increase the number of Oregonians eligible to receive medical treatments through the state's Medicaid program by covering all persons up to the poverty line. The legislature recognized that, operating within a fixed Medicaid budget, those to be covered could not have all the medical services they wanted. They could have only

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what the state could afford. Medical procedures were ranked according to priorities determined by the three criteria of cost-effectiveness, quality-adjusted life years, and the expressed values of the people of Oregon. The state then went down this list as far as it could until its resources had been expended. Services below this line were not to be available.[2,3]

Thirty bioethicists were invited to participate in the last two months of the discussions leading up to the speech President Clinton delivered to a joint session of Congress in which he outlined the objectives of his health care reform proposal. They were expressly instructed not to consider rationing.[4] There was to be no recognition of the elementary fact that in a system of universal coverage that is operating within a fixed budget, hard choices will have to be made about what services are to be available, when, and for whom.

Compounding this fatal flaw in the proposals now beginning to be debated in Congress is the way the word "quality" seems to be used as a synonym for "quantity." The quality of the present system must be and will be maintained, we are told. Translated, this means that we will continue to receive whatever we have become accustomed to. There will be no cutting back on the array of services to be provided.

Underlying this deliberate avoidance of the subject of rationing, or any discussion of limits, is a political capitulation to a popular misconception of the nature of autonomy. In the writings of John Stuart Mill and Immanuel Kant, autonomy is construed as a negative right to noninterference in matters of personal choice and private self-determination—with the sole proviso that one's choices ought not to harm or endanger others.[5] What began as a negative right to noninterference has commonly come to be thought of as a positive entitlement—the right to have whatever we want, especially if someone else is paying for it. Rather than the current proposals for health care reform challenging this distortion of the original meaning of autonomy, they accommodate it.

Limits must be considered if costs are to be held down and universal access to the system is to be guaranteed. Quality can and must be maintained, but not quantity. Marginally beneficial or useless treatments are inimical to quality medical care. Yet these are what patients, their families, or their physicians often want. Autonomy, misconstrued, cannot subvert the principle of distributive justice.

If the three goals of holding down costs, including all Americans in the health care system, and assuring quality are to be met, the three patients described at the beginning of my article would not receive the care they did. Yet another example is to be found in neonatology. In neonatal intensive care units, we continue aggressively to treat infants weighing less than 750 grams at birth, whose gestational age is barely 24 to 26 weeks. This is exorbitantly costly, and the results are not encouraging. Only about a third of these infants survive; of those who do survive, about 50% are moderately to profoundly damaged—neurologically as well as physiologically. Will intensive care for this category of infants continue to be available in a system of universal access within a global budget? Or, as I have argued,[6] ought this to be designated and funded as research and offered only to a limited number of patients on an experimental basis?

For refusing to consider or to allow the consideration of rationing, the current proposals fail. But the failure is not the politicians' alone. They are merely responding to what they perceive to be the will of the American people. Ultimately, the failure is ours. Daniel Callahan puts his finger on it:

> What might be called the death fallacy the notion that our mortality should be wholly under our control—has two components, one moral, the other medical. The moral part is the belief that we have an unlimited obligation to combat death and lethal disease. . . . The medical part is the potent assumption that death is essentially an accident, correctable with enough money, will, and scientific ingenuity. . . . In other industrial countries neither a very-low-birth-weight baby nor a seriously ill elderly person is likely to be subjected to aggressive treatment. They have made the judgment that in certain cases the price of continued treatment is simply too burdensome to the patient and to society ("Our Fear of Dying," *Newsweek*, October 4, 1993, p 67).

We have failed to make that judgment. Until we do, the laudable goals of simultaneously holding down medical expenditures, ensuring universal access to the system, and maintaining its quality will continue to elude us.

This leads to the hard questions: by what ethical criteria and by what methods can services be limited? As a basis for further discussion, let me respond briefly to these two questions.

Ethical Criteria for Limiting Services

We have to learn to distinguish needs from wants. It was perhaps easier for the British to do this when the National Health Service was launched in 1948 than it is for us now in 1994. Before 1948, the British had fought a long, debilitating war from 1939 to 1945. During these years, rationing of food, fuel, and clothing was commonly accepted. Austerity did not end with the war. The postwar years required a British contribution to the rebuilding of Europe. The available resources were needed to provide necessities; little was left over for luxuries.

Our situation in 1994 is vastly different. In 1959, when the Stanford Medical Center moved from San Francisco to the main campus and a new hospital was opened, it did not have a single intensive care bed. Today there are more than 200. The 1960s, 1970s, and 1980s saw the expansion of high-technology, high-cost intensive care medicine in the United States. Luxuries came to be thought of as necessities. Wants came to be equated with needs. Drawing a distinction between the two categories as we embark on a new health care system is clearly much more daunting a task for us than it was for the British in 1948. Nevertheless, this is the challenge we all now face—not only in health, but also in such areas as transportation, education, and housing.

Even if we were able to distinguish between needs and wants (perhaps the first criterion for rationing), we are left with a further difficulty. Because of what might be called the genetic and social lotteries, people have widely

differing medical needs. How might those with exceptional medical needs be justly served if rationing is inevitable? Distributive justice is at issue here. Any plan to limit services must be consistent with this cardinal ethical principle.

My most radical criticism of the current proposals for health care reform is that they are predicated on universal access to the same basic package of benefits for all—a single-tier system.

Perhaps what is needed is a three-tier system consisting of the following:

- Universal access to basic medical services, with the emphasis on primary care, preventive medicine, and health promotion.
- Access to a more limited array of medical, surgical, and psychiatric services for those with exceptional or catastrophic needs caused by the genetic and social lotteries.
- Supplemental services not included in the basic package and not qualifying as catastrophic that could be purchased through insurance by those who can afford to do this.

Only then will people be fairly treated, according to need.

Defining basic medical services and services for exceptional or catastrophic needs will be the challenge. How might this be done? Before addressing that question, let me remark on what I consider to be an ethically unacceptable criterion for rationing, that of chronologic age.

A number of writers find age an attractive standard for rationing.[7-9] The popular argument is that in Britain, under the National Health Service, persons older than 55 years are not eligible for regular hemodialysis or for renal transplantation. Why should we not ration services in the same way?

It is not true that in the United Kingdom age is the basis for rationing. There is no policy limiting the use of long-term hemodialysis and renal transplantation to persons younger than 55. General practitioners decide whether or not to recommend persons older than 55 for these services on the basis of an assessment of their patients' overall health and the availability of resources in the region. It is true that the recommendation for dialysis or transplantation generally is not made for older patients.

Physiologic reserve (the health and vitality of the major organ systems added up and taken together) rather than chronologic age is a sounder criterion for rationing costly services. Persons in their 40s may have little physiologic reserve. Conversely, there are those in their 80s whose physiologic reserve is considerable. No moral objection can be made to physiologic reserve being used as a criterion for admission to intensive care units or to determine eligibility for other high-cost, high-technology, acute medical services.

Methods for Limiting Services

Demographics and epidemiology will be important in the attempt to limit services. Both disciplines can provide indications of the principal needs of the population generally, as a guide to setting priorities. Beyond this, there is much to learn from the Oregon experiment. Better outcome data—both for efficacy and cost—for common as well as uncommon interventions are necessary. Estimates of improved morbidity and mortality resulting from various interventions can and must be made. The concept of quality-adjusted life years may be a first step in the right direction. And the American people have to be involved in the process of ranking services according to their own preferences and values. Only as citizens share in formulating health policy proposals through a democratic process of participation in surveys, questionnaires, and town meetings can they be expected to accept and abide by the limits that eventually are established.

A further urgent imperative is that the medical profession must begin more rigorously to define appropriate standards of care in various diagnostic categories. The examples I gave at the beginning of this article illustrate what will not be possible if the three goals of affording universal access, holding down costs, and assuring quality are to be met:

- The high-risk cardiovascular surgery patient who received 750 units of blood in the five days before he died had been turned down by two other medical centers before being accepted by a third. This suggests that selection criteria for high-risk procedures need to be more carefully defined nationally and applied locally.
- Assuming that liver transplantation is included in a list of priorities for services available to those with catastrophic needs, how many organs should a single patient receive? Ought this decision be made on the basis of past investment in a given patient or on the unmet needs of others awaiting transplantation? Those doing transplantations must address this issue at a policy level.
- What is the standard of care for patients in a persistent vegetative state? There is no medically agreed-on answer to this question. Hence, a nephrologist who believes hemodialysis for such a patient to be inappropriate is out on a limb—subject to the threats and manipulations of family members whose wants are being denied. Here, too, the profession must back physicians attempting to make hard choices by developing a more universal consensus about what is and what is not medically appropriate.[10,11]
- Whether neonatal intensive care continues to be available for infants weighing less than 750 grams with a gestational age of 24 to 26 weeks also needs to be decided by subspecialists in this field after an informed and deliberate review of the outcome data at the national level.

Rationing is possible, and it can be done ethically. It will require acceptance of a three-tier system of medical services. Which services qualify as basic and which as catastrophic will have to be decided on the basis of demographic, epidemiologic, and outcome data; estimates of quality-adjusted life years; the values and preferences of the American people; and last, but not least, the medical profession defining the limits of appropriate treatments in various diagnostic categories.

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Special Series

Primary and Managed Care
Ingredients for Health Care Reform

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The use of primary and managed care is likely to increase under proposed federal health care reform. I review the definition of primary care and primary care physicians and show that this delivery model can affect access to medical care, the cost of treatment, and the quality of services. Because the use of primary care is often greater in managed care than in fee-for-service, I compare the two insurance systems to further understand the delivery of primary care. Research suggests that primary care can help meet the goal of providing accessible, cost-effective, and high-quality care, but that changes in medical education and marketplace incentives will be needed to encourage students and trained physicians to enter this field.

(Bindman AB: Primary and managed care—Ingredients for health care reform. West J Med 1994; 161:78-82)

The Clinton Proposal for health care reform emphasizes the primary care delivery model.[1] It offers strategies to increase the relative supply of generalists versus specialists and creates incentives for patients to choose managed care, which fosters primary care to a greater degree than traditional fee-for-service. Whereas the rapid growth in managed care suggests that even without reform, the marketplace will shift toward primary care, only recently have many physicians and health policy analysts begun to analyze this trend and to assess the likelihood that this shift will improve our health care system.

This trend raises several fundamental questions. What is primary care? Who is a primary care physician? Does primary care improve access to medical care? Does it improve quality? Finally, does it reduce costs? Rather than summarize all of the research that addresses these issues, this article highlights the findings from several well-done studies.

Defining Primary Care and Primary Care Physicians

During the 20th century we have seen an evolution in the definition of primary care. In the 1920s it was described as first-contact care.[2] The definition was expanded in the 1960s to include its longitudinal and comprehensive aspects.[3] The most complete definition to date was developed during a consensus conference at the Institute of Medicine in the late 1970s.[4] That statement identified five fundamental components: accessibility, accountability, comprehensiveness, continuity, and coordination.

Accessibility refers to the availability of health care services and a person's ability to use those services. Accountability is the degree to which a physician takes responsibility for a patient. Comprehensiveness addresses the breadth of problems a physician manages, including those involving multiple organ systems at varying levels of service from prevention to care for chronic illness. Continuity focuses on longitudinal care and the notion of an evolving record that facilitates a prospective strategy for patient care. Coordination describes the integrative function primary care physicians perform in ordering and reviewing tests and consultations.

Defining who is a primary care physician has been debated for more than a decade.[5,6] and the Institute of Medicine's definition does not specify which subsets of physicians deserve this title. Under federal health care reform such a distinction may be associated with financial gain; not surprisingly, physicians from a wide range of specialties have been lobbying to be considered primary care physicians.

Weiner and Starfield have offered an empirical approach to resolve this debate.[7] They reviewed actual practices of different specialists and measured how well they met certain features of primary care. Judging physicians according to how many of their patients were self-referred and by the accessibility and comprehensiveness of services provided, they found that family and general practitioners, general internists, and general pediatricians were more likely than other specialists to provide primary care. Obstetrician-gynecologists ranked the next highest, above internal medicine subspecialists, general surgeons, surgical subspecialists, and psychiatrists. Health policies have

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incorporated this type of empirical assessment, as is evident from the current Clinton proposal, which endorses a broad definition of primary care and recognizes family and general practitioners, general internists, general pediatricians, and obstetrician-gynecologists as primary care physicians.

Only a third of physicians in the United States identify themselves as primary care physicians, far less than in most other industrialized countries, including Australia (44%), Canada (52%), Germany (54%), and the United Kingdom (63%).[8] But specialists have not always predominated in the United States. Although generalist physicians made up 50% of the total in the United States in the early 1960s, the proportion of specialists has grown dramatically since then (Figure 1).[9] Particularly in low-income areas, office-based primary care physicians have nearly disappeared, dropping by 45% in poor urban settings compared with a decrease of 27% in more affluent communities.[10] During the same period, the total number of physicians grew by more than a third.

The United States has more physicians per capita than most other industrialized nations, but they are distributed

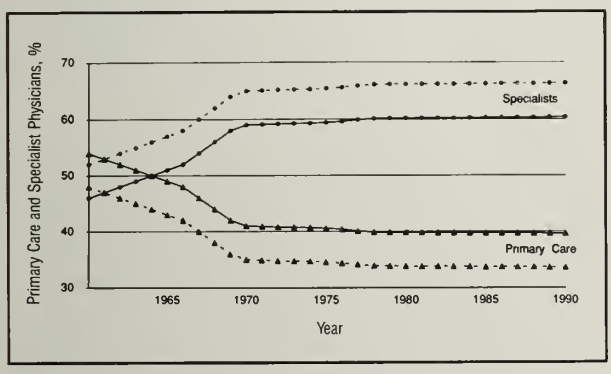

Figure 1.—The total number of all physicians—not just member physicians—by specialty is derived from annual reports produced by the American Medical Association (from Roback et al[9]). The designation of primary care versus specialist physician is according to the author's description. Primary care: -▲- = family practice, general internal medicine, pediatrics, and obstetrics-gynecology; -▲- = family practice, general practice, general internal medicine, and pediatrics; Specialists: -●- = all nonprimary care specialties; -●- = all nonprimary care specialties and obstetrics-gynecology

unevenly both geographically and by specialty. This is the case even when the definition of primary care physician is extended beyond family and general practitioners, general internists, and general pediatricians to include obstetrician-gynecologists.

Primary Care and Access

The number and distribution of physicians can influence how patients receive health care. For example, as the number of primary care physicians has dwindled, the number of emergency department visits has increased.[11] In one study Medicaid patients were randomly assigned to two groups: one had a primary care physician and the other did not. The first group had substantially fewer emergency department visits without an accompanying increase in the use of a primary care physician's office.[12] Perhaps patients with primary care physicians had their problems managed by telephone or felt reassured that a physician was available if needed.

Access to primary care also affects health outcome. According to one report, the predominant reason patients with uncontrolled hypertension either sought treatment at an emergency department or were admitted to a hospital was the lack of a primary care physician. This was an independent and more significant risk factor for a hypertensive emergency than uninsured status or noncompliance with medical therapy.[13]

Patients may not have primary care physicians because physicians are unwilling to accept them, as is often the case with uninsured or Medicaid patients. In this respect primary care physicians do not seem different from specialists. In a national survey of physicians, family practitioners (82%), internists (80%), pediatricians (81%), and obstetrician-gynecologists (73%) showed no more willingness to accept Medicaid patients than other physicians (84%).[14] A 1993 survey in California found that only 31% of family and general practitioners and general internists were willing to accept new Medicaid patients into their practice.[15]

Primary care can reduce the use of emergency departments and improve health by controlling recurring medical conditions. As more patients who are uninsured and underinsured are brought into the health care system, the demand for primary care physicians will increase. Health policies will influence whether that demand is met by retraining specialists, training more generalists, increasing the pool of nonphysician practitioners, or a combination of all three approaches.

Primary Care and Cost

The federal government's interest in a primary care delivery model probably stems from a belief that primary care is less expensive than specialty medicine, not only in terms of direct payments to physicians, but also because generalists tend to use fewer resources than specialists. In 1992 the average generalist earned $113,000 while the average specialist made $183,000.[16] Even if generalists made up 50% rather than 36% of physicians, the savings in direct payments would be $5 billion, a savings of only .5% to 1% of the trillion dollars we spend on our health care system.[17]

Of greater importance are the cost differences associated with practice pattern variations. The literature on how generalists and specialists practice medicine is extensive but difficult to interpret because of the differences in the types of patients who see each class of physician. Although specialists tend to see sicker patients, studies that have avoided selection bias or adjusted for differences in patient populations have found that primary care physicians use fewer technologies and admit patients to the hospital less frequently. One study done on a medical ward service at a university teaching hospital over a three-year period looked at whether the specialty of the attending physician affected the number of procedures ordered.

It was found that when the ward team was headed by a subspecialist as opposed to a generalist, a substantially greater number of colonoscopies, bone marrow biopsies, exercise treadmill tests, and other procedures were ordered.[18]

Perhaps the study that best examines the differences in practice patterns between specialists and generalists is the Medical Outcomes Study, because it adjusts for the variation in severity of illness among patients with cardiac disease and diabetes mellitis who see family practitioners, general internists, endocrinologists, and cardiologists.[19] These researchers found that the number of office visits, the percentage of patients tested per visit, and the percentage of patients admitted to the hospital were higher among specialists than among generalists.

In one of the only studies to look at preventive care, Dietrich and Goldberg found that generalists and specialists did not use these services differently and that both groups fell short of preventive guideline recommendations.[20]

Primary Care and Quality

Do patients fare better when seen by specialists than by generalists? The answer, although critical to assess the importance of differences in resource use rates, is not really known. Poor technique limits the reliability of the few randomized studies done. For example, in a study of asthma patients, it was found that those assigned from an emergency department to pulmonologists had better outcomes than those assigned to generalists.[21] The validity of this finding is questionable, however, because the pulmonologists treated the patients according to a protocol not given to the generalists.

Specialists do seem to achieve better results than generalists when treating patients with problems within their specialty. But studies of this do little to control for patient differences, and there is equally strong evidence that specialists do less well outside their specialty area[22] and refer less appropriately than do generalists.[23] This suggests that if they are to make up for the deficit in primary care physicians, specialists will require retraining.

Primary and Managed Care

Despite the absence of definitive evidence that primary care can lower cost and preserve quality, managed care organizations have rapidly adopted this delivery model. Managed care organizations oversee networks of physicians through individual practice associations, preferred physician organizations, and health maintenance organizations (HMOs). They (particularly HMOs) rely on primary care gatekeepers to control costs and resource use. Because more primary care is used in a managed care system than in fee-for-service,[24] comparing the two insurance systems can shed some light on differences in the delivery of medical care.

Substituting primary care for specialty care in the managed care setting affects the number and type of physicians needed. Such plans employ substantially fewer internal medicine subspecialists than are generally used in fee-for-service medicine. The physician staffing patterns of a typical group model HMO were compared with the number of physicians available in the national physician supply pool. Representation for every internal medicine subspecialty was consistently greater in the fee-for-service environment than in a typical HMO, yielding the following per capita ratios: cardiologists, 2.0; gastroenterologists, 1.9; pulmonologists, 1.7; nephrologists, 1.6; rheumatologists, 1.5; hematologist-oncologists, 1.5; infectious disease specialists, 1.3; and endocrinologists, 1.3.[25]

Managed Care and Quality

Is quality preserved when managed care plans use a primary care delivery model? Again, little research addresses this question. In studies that controlled for patient differences, health outcomes have been as good or better in managed care as in fee-for-service.[26,27] The Rand Health Insurance Experiment randomly assigned several hundred participants to either HMO or fee-for-service insurance. Patients with incomes above the median had significantly better health outcomes in HMOs than in a fee-for-service setting.[28] In contrast, patients with low incomes had poorer outcomes, suggesting that different types of patients may benefit from different delivery systems. It was further reported that managed care patients are less satisfied with their care than fee-for-service patients.[29]

Managed Care and Cost

The business community has embraced the primary care model within many managed care plans because it appears to save money. A 1993 survey of employers found that HMO premiums were about 7% less than those for fee-for-service insurance.[30] Employer and individual contributions to premiums averaged $158 per month for persons in HMO plans and $170 per month in fee-for-service plans. Although HMO coverage has been less expensive than fee-for-service insurance for the past few years, premiums for both have risen at similar rates, raising the question of whether savings from managed care is a one-time event or can be expected to continue.[31] Data on health insurance are based on the charges for premiums and do not reveal the true cost of providing care. Operating costs for managed care could be considerably lower than the premiums reflect as companies set prices below those of fee-for-service plans to make them attractive to consumers while still achieving the maximum profit.

Two unresolved questions remain. First, is managed care less expensive than fee-for-service health care because of an advantage in efficiency or because of selection bias? A number of studies have shown that a younger and healthier population elects HMO rather than fee-for-service coverage, demonstrating the potential for selection bias to explain cost differences in plans.

Second, does a primary care model increase savings beyond the level projected for managed care alone? In a randomized trial within a managed care plan, it was found that patients assigned a primary care gatekeeper had considerably lower ambulatory care charges ($21 per person each year) than those not assigned a primary care physi-

cian, but that hospital and total health care costs did not differ significantly.[32]

Even if managed care does not clearly save money over traditional fee-for-service insurance, it offers the political benefit of sidestepping an explicit public discussion of rationing. Capitated payments under managed care force the health plan and the physician, rather than the government, to decide how care should be allocated. The public has generally opposed rationing of health care, yet it has increasingly accepted managed care plans that limit access to certain services.[33]

Medicine's Response

Anticipating the growing market demand for generalist physicians, the Federated Council for Internal Medicine has recommended that 50% of graduates from internal medicine residency programs enter the practice of general internal medicine.[34] Even if 50% of all medical students were to immediately enter generalist fields, however, it would take almost 50 years to reach the point at which the overall pool of physicians would consist of 50% generalists.[35]

Although the leadership within internal medicine has endorsed generalist training, the residency choices of students often undercut this policy. Between 1986 and 1994 the number of US medical school graduates matched to internal medicine residency positions declined by more than 30%.[36] There are many reasons for this decrease in interest, including higher salaries in other fields, a perception of a better lifestyle for specialists versus generalists, and a lack of generalist role models for students in many medical schools. Although most deny the effect of anticipated income on their choice of specialty, a strong statistical association has been shown between the income of a specialty and the percentage of residency positions filled in that specialty.[37] The primary care fields of internal medicine, family medicine, and pediatrics are among the lowest paying.

The medical school curriculum and admission methods can also influence a student's decision. Jefferson Medical College (Philadelphia, Pennsylvania) has increased the number of its graduates who become generalists by designing a recruiting process that attracts students interested in primary care.[38] Medical schools that have a department of family medicine and less federal research funding produce more generalists, suggesting the importance of specific role models in influencing career choice.[39] The type of internal medicine training program is also associated with a resident's decision to subspecialize. Nationwide, 60% of categorical internal medicine residents elect to subspecialize,[40] while only 28% of those in primary care internal medicine residencies choose to do so.[41] While these differences suggest a training approach that can encourage the development of more general internists, at least part of the difference is most likely attributable to student selection. Primary care positions constitute about 10% of all internal medicine residency positions, making their current impact on generalist training small. Whether an expansion of primary care programs can induce student demand is unknown.

Conclusion

Perceiving that the primary care model can provide cost-effective, high-quality service, the marketplace is demanding more generalist physicians. Although research does not provide overwhelming support for such a change, it does offer encouragement. The leadership of internal medicine (among others) has embraced the training of generalist physicians.To induce medical students, however, to select primary care training will require alterations in the medical school student selection process and medical school and residency curricula. Training programs will have to invest in faculty who can teach primary care. Finally, salaries across specialties will have to become more equitable, a process that has begun to occur within HMOs and with the passage of Medicare's resource-based relative value scale fee schedule.

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A Conversation About Health Care Reform

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The following edited conversation between Professor Fuchs and Linda Hawes Clever, MD, Editor of the journal, took place on April 8, 1994.

LHC: *What is the most important goal of health care reform?*

VRF: It is to slow the rate of growth of health care expenditures.

LHC: *Is universal coverage not important?*

VRF: It is important, but secondary in political importance. Many persons favor it as an abstract concept, but are unwilling to support the subsidies and compulsion required to achieve it. If health care spending was not increasing 3% per year faster than the rest of the economy, I do not think you would be able to mount great political interest in health care reform.

LHC: *So the real interest is on the part of the businesses that are just spending too much and cannot stand it.*

VRF: Not only or even especially business. The government sees the health care part of the budget growing so much faster than everything else. As President Clinton said at the economic summit, unless he could do something about health care, everything else we are talking about does not matter.

LHC: *What is wrong with spending 15% of the gross national product on health care?*

VRF: Nothing, provided three conditions are met:

- The services that are being provided must be worth what they cost. If many are not, then there is a case for reducing the spending.
- The services must be produced as efficiently as possible. If the services are worthwhile, but we are wasting a lot of resources, human and capital, in producing them, then we will worry about how much we are spending.
- The resources being used to produce the services—the physicians, the nurses, the capital equipment, the drugs, and so forth—must be priced fairly. They should be getting a true competitive rate of return, but not more. If there are monopoly rents and monopoly profits being earned, there is a reason for concern.

LHC: *Do you think health care is being held to a higher standard or different standard from other enterprises?*

VRF: No. For the most part, it has been held to a lower standard. Nobody imagines for a moment that we ought to be producing the best possible cars of the highest quality regardless of what they cost. Nobody believes that we should be producing the best possible electronic equipment, or things of that kind. The problem is that third-party payment—insurance—has put health care in a very special category. Now, are there other sectors where the same kinds of questions could be raised? The defense sector is certainly one of them.

LHC: *What should the rate of growth of health care costs be?*

VRF: Again, if the three conditions were met, there would be no reason to be concerned that health care spending is growing more rapidly than the rest of the economy. We do not worry if automobile spending is growing more rapidly or if spending for computers is growing more rapidly because we think that within reasonable tolerance limits, those three conditions are being met. So, there is nothing specifically wrong with the rate of growth.

(Fuchs VR: A conversation about health care reform. West J Med 1994; 161:83-86)

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Once health care costs get to be 1/7 or 1/6 of the total economy, however, if they continue to grow a lot faster than the rest of the economy, it does begin to provoke certain kinds of strains, and you are going to get reactions elsewhere. But fundamentally, there is nothing really wrong with any particular rate of growth. Given the fact that there is this 3% gap and it has been there for 40 years, I think the target over the next decade will be to try to bring that 3% gap down to 2% or 1%, and, of course, some people talk about bringing it down to parity with the rest of the economy. What the gap ought to be really depends on getting those other three things right.

LHC: *Who will declare the "correct" size of the gap, and, even more basically, who will define "appropriate care"? One of the things that physicians are concerned about is to make sure that they are involved, too, not just researchers and not just economists.*

VRF: I agree entirely. I have never thought that economics or any other external discipline ought to be providing the answers. What we ought to be doing is trying to redirect the questions. The answers ought to be coming out of medicine itself.

LHC: *I think that what is worrisome to physicians is the transition.*

VRF: Physicians' concern about the transition is influenced by many factors: relationships with patients, fear of malpractice suits, worries about maintaining their incomes. All these concerns tend to get merged, and it is difficult for physicians to sort out their real feelings.

LHC: *Where do insurance companies fit in health care reform? Do they have to fit into the plan?*

VRF: There has to be insurance. After all, the Kaiser Plan is an insurance company, along with being other things. The risks are being shared so that individuals do not have to bear the full cost of their own illnesses. To that extent, the insurance function must be fulfilled. Associated functions such as the servicing of claims and so on also have to be performed. Insurance companies today do not always provide insurance. Many employers are self-insured; insurance companies provide administrative services only. So, under any system, both things, the risk pooling and the administrative services, are going to have to be done. I am concerned about having these integrated health systems—the systems that combine hospitals and physicians and prescription drugs and possibly other services—being led by profit-seeking companies. Having them led by health professionals, particularly physicians, is preferable. Many of the most successful large-scale medical enterprises in the country, such as the Mayo Clinic or the Kaiser Plan or the Group Health Cooperative in Seattle, are characterized by a substantial amount of physician leadership.

LHC: *It has been said that prevention costs more money than it saves.*

VRF: Most studies show that even where preventive activities are good from a health perspective, they usually do not reduce expenditures for health care. We usually wind up having spent more money for health care, and the additional spending can be very large. You can imagine that, for example, if we began a large-scale national screening of cholesterol and lipid levels and treated every abnormal finding very aggressively, the increased expenditures would be great. One of the leading authorities on the economics of prevention is Louise Russell of Rutgers University. Her conclusions have been confirmed by other evidence using entirely different approaches.

LHC: *But then, there is more to life than saving money, and the question is how do you weigh values? It has been said, for example, that the most cost-effective thing that you can do to save health care expenditures is to kill all babies.*

VRF: To say you are going to kill all babies or you are going to kill off everybody over 70 is completely ignoring the value of life to those you have killed. And economists would never recommend that. An economist would say that those values are part of what goes into the health care equation.

LHC: *It seems as if some companies want only to save money. The value of health, the value of a life, or the value of nonsuffering is not included in their calculations.*

VRF: That may be, but, if so, it is wrong. It should not be. But what you may hear from time to time is a frustration on the part of the nonmedical community about the unwillingness of many physicians to confront the legitimacy of concern over the cost of medical care. There is a huge difference between saying this is a legitimate concern that ought to come into calculations along with other things and going to the wild extreme and saying cost is the only thing we ought to be concerned about.

LHC: *Let us talk about tort reform. Do you think it is an important part of health care reform?*

VRF: I think it is moderately important to get a handle on unreasonable malpractice suits and excessive awards. I do not think it is as important as most physicians do, judging from questions that I get at meetings, but it is terribly important symbolically because as long as physicians can say, "Oh, we do this because of the fear of malpractice," it stands in the way of reaching a more rational system of delivery. It is moderately important in economic terms, but terribly, terribly important from the point of view of getting physicians behind the changes.

LHC: *You have been outspoken about not linking health insurance to employment. Talk about the "employment link."*

VRF: The employment link that is preserved in the Clinton Plan is not a charade exactly, but it is an illusion. The plan really aims at a de facto separation of employment and insurance. But President Clinton wants to preserve

the illusion and the paraphernalia of an employment-based system. This has been judged to be the most salable way to go toward universal coverage. I am not in a position to judge the political salability of things. I can only look at the plan and see that it is a tortured, convoluted way to achieve de facto separation while making it seem as if it is still an employment-based system.

First of all, there can never be universal coverage unless you have individual mandates to go with the employment mandates. And there will be a lot of cross-subsidizing of all kinds. A real employment-based system is one in which each employer is responsible for the health care of his or her employees. In the Clinton Plan, nearly everyone is going into a pool. The employer is not going to choose the insurance options. The employer basically is going to pay a tax. If we had a system based on a payroll tax, or if we had a system based on a value-added tax, there is no more reason to call one an employment-based system than the other.

LHC: *A lot of resistance is coming from employers because they believe that much of the burden is going to be put on them.*

VRF: We know that there is a lot of talk and a lot of fuss about that. I think that we pay too much attention to the resistance to change, and we credit it with too much substantive importance. We should not exaggerate the amount of real harm and damage that is being done. It is easier to yell a lot than to make the change. Going to a different system is not going to be painless or costless to employers. On the other hand, the fact that they yell a lot does not tell me that the cost is going to be great.

LHC: *A lot of heat and not much light.*

VRF: That is right. One group where one can see a definite and immediate effect is the group that employs workers at or close to the minimum wage. If you are employing people and paying them $9,000 or $10,000 a year in salary, and you suddenly have to add another $4,000 for health insurance, that is a 40% increase in the cost of their labor. We have no experience with increases of that magnitude. When we increase the minimum wage, we may increase it by 25 cents an hour or something like that. With the large increases implied by health insurance, employers of low-wage workers will have to let some of them go because they cannot absorb that kind of increase, nor will they find it easy to pass all of the cost on to their customers. In this case, there is real substance behind the heat.

LHC: *Then there is the proposal to subsidize minimum-wage employers.*

VRF: Yes, it is based on the size of the employer, which makes no sense to me at all. I have always been in favor of subsidizing low-income persons. But the way that the Clinton Plan and several of the other plans choose to subsidize is very inefficient. It is inefficient for two reasons. First, it is going to be very costly to administer subsidies based on individual incomes. You have to gather enormous amounts of information if you want to enforce the law fairly and completely. You have to spend a great deal on enforcement because there is a great temptation to work off the books or to evade the income tax.

The other bad feature is that even where you put aside the administrative cost, the enforcement cost, and the evasions, you are putting low-income people into a high marginal tax bracket because they lose the subsidy as their income increases. I will give you some concrete figures. Let us say that a family at a poverty level of $14,000 a year is going to get full subsidy, which is worth $5,000 for family insurance. Now, at $28,000, which is double the poverty level, the subsidy disappears. And in between, it goes down as income goes up. So of that additional $14,000 that a family is going to earn, it is going to pay income tax on that amount. It is going to pay Social Security tax on it. That family is going to lose its earned income tax credit, and it is going to lose $5,000 worth of health insurance. Henry Aaron made a calculation on the Cooper Plan that the people who go from poverty to twice poverty will face a marginal tax rate of 84%; they will keep 16 cents out of every additional dollar that they earn. That is not much incentive to try to improve earnings, to get a better job, to work, or to move. And that is a fundamental weakness in all plans that subsidize individuals based on their income.

LHC: *How should they be subsidized?*

VRF: The approach that I favor is to provide them with insurance financed by a general tax so that the subsidy is more elastic. For instance, if it is an earmarked value-added tax, the more you spend, the more you are contributing to the financing of health care. But the implicit subsidy declines in proportion to your spending. It does not disappear. You do not have $5,000 suddenly disappear between $14,000 and $28,000 of income. Let us say the tax is 5%, then 5% would disappear by virtue of your additional spending. Moreover, it cannot be evaded. It does not matter whether you are working off the books or whether you got the money from your father-in-law, or whatever. If you are spending, you are paying.

LHC: *What's the resistance to a value-added tax?*

VRF: Taxes are not popular. It makes it more evident that you are paying for it. The name of the game politically seems to be to make people think that somebody else is paying for it. But a mandate is a tax.

LHC: *What about cost sharing as a way of keeping down health care expenditures?*

VRF: You mean copayment?

LHC: *Yes.*

VRF: I have always felt that a modest copayment done in the simplest manner from an administrative point of view is a worthwhile thing to keep a patient involved and aware that medical care does cost money. What do I mean? I

mean something like $10 every time you go to the doctor or $5 every time you get a prescription filled. But if it is something that is going to involve elaborate record-keeping, bookkeeping, billing, things like that, it is not worth it.

LHC: *Copayments discourage the use of medical care by poor people, people who cannot even pay their bus fare.*

VRF: Well, if you had a modest copayment, like $10 a physician visit and $5 a prescription, you could leave it to the plan to have a special provision to waive the copayment for very poor people.

LHC: *Is including long-term care, which is primarily social care, going to sink the plan? Should it be included in a medical plan, or should there be a whole other structure?*

VRF: It is important at this point to establish the principle of universal coverage equitably financed within an organization-and-delivery framework that can come closer to the appropriate rate of growth of health care spending. Once that has been done, we could think about expanding the scope of benefits and things of that kind. It is going to be difficult enough to do that, and it is asking too much to do everything right from the start.

LHC: *One of the things that I am concerned about is medical education. Right now. And research. Right now. I have a concern that important programs are being adversely affected.*

VRF: They are. And they should be. Medical education has never taken seriously the kind of questions that we have been discussing up until now. The people who run the divisions and departments of medicine need to sit down and say, "What kinds of educational programs should we have for the kind of health care system that we see evolving?" I would be reluctant to try to maintain medical education as it is. In medical education, it is customary to take the cost of education as a given and to ask, how can we find the money to fund it? Rather, we should start asking, what are we trying to accomplish and are there ways of accomplishing it at a lower cost? Or to ask an even more important question: are we trying to accomplish what we ought to be trying to accomplish?

For example, the division of cardiology at Stanford University has an imaginative new approach. Rather than coming purely from thinking about education, it is an approach that comes from thinking about the delivery of services to patients in the community, working backwards to the kinds of educational and research programs that we ought to have. Medical education should be planned with careful thought, starting with consideration of the needs of patients and of society. The problem with education and research up until now is that as long as the money was available, it was a top-down-driven system.

LHC: *Do you have any comments about the role of nurse practitioners and physician assistants in health care?*

VRF: I was very enthusiastic about physician extenders 20 years ago. My reading of the literature at that time said that there were many settings and situations where physician extenders working under physician supervision could do as well as physicians at lower costs. The country decided to go the other way—to expand greatly the number of physicians. This has led me to say that the physician extender is a solution whose time has passed. As long as you had all those physicians out there, there was no room for extenders because physicians had to make a living first. We are coming again to a time when we need to reconsider. Patients seek medical care for a continuum of conditions and needs and require a continuum of personnel to meet those needs. There are many times when a patient's needs could be better met by someone who has more time to spend because their time is less expensive, someone who can communicate with patients in their own language or vocabulary or idiom and who is sensitive to the problems that patients may face at home or on the job or in their relationships. So, yes, I am in favor of physician extenders, but in a setting where there is supervision, where there are protocols, and where there are checks and balances and opportunities for referral and consultation.

LHC: *As you know, a number of states allow independent practices for nurse practitioners.*

VRF: Once we have integrated health care plans, supervision will come back. There will be no scope for individual physician extenders any more than there will be scope for physicians in solo practice.

LHC: *On the specialist-subspecialist issue, do you have any thoughts?*

VRF: Yes. In many specialties there is not enough work to keep physicians busy in their specialties. That was true when I studied general surgeons 20 years ago, and it is still true. I do not think one can give general answers to this, however, because it depends on what kind of disease and what kind of patient we are talking about. For example, in diabetes it may be that the best combination is an endocrinologist, working with physician-extender specialists in diabetes, as opposed to a general practitioner who is neither one nor the other. So it all depends on the disease and the patient.

LHC: *It would be very nice if we could have the luxury and the opportunity of doing some of this fine-tuning.*

VRF: Let me leave you with a final thought. The intellectual challenge to academic medicine has never been greater than it is today: how do you organize to deliver the most effective care, and what kinds of interventions are most effective in what settings with what kind of personnel? When you develop new technologies, bear in mind how you are going to deliver them and at what cost. The creative, scientific, and intellectual challenges are enormous. Basic science needs to continue, and basic scientists go where the ideas go. But there needs to be better communication among basic science, the practice of medicine, and the needs of patients.

Editorials

In the Meantime

HEALTH CARE REFORM is years away. In the meantime, we have health care revolution. As with all revolutions, important matters are not receiving enough attention. One of the most neglected issues is the fate of medical education and research and of teaching institutions. There is plenty of talk about the training of specialists and subspecialists. What about medical students? Surely we have not seen the last of physicians who take simple pleasure in listening to patients (and their hearts) because they can discover important information from the endeavor.

Glaser is concerned that the lack of intense, long-term hospital experience will impair students' abilities to learn how to do a thorough history and physical examination and to learn the natural history of disease.[1] Perhaps rotations through hospices, nursing homes, rehabilitation centers, and home care programs could help.

Aside from the teaching site, however, who will teach medical students the art of history taking and physical diagnosis? We know that these outshine all of technology in determining a patient's diagnosis and prognosis.[2] Who will teach patient education and counseling? Who will teach warm-hearted skills that build trust and are essential to healing? Who will teach about values and practical ethics? As primary care clinicians rush through an increased load of patients, will subspecialists be willing or able to teach the basics? Is there a place for displaced physicians, for physicians with superlative skills who take good care of patients in the old-fashioned way—with more time and less technology—to teach medical students and house officers? Should these and other teachers be paid for teaching time away from their office practices when they thereby lose income? Who will pay them?

Another threatened essential is clinical research. We must continue to learn so we can contend better with the known and unknown. Science has not conquered nature. Some enterococci now respond to no single antibiotic or combination of antibiotics. Multiple drug-resistant tuberculosis is killing patients and health care workers. Breast and prostate cancers are epidemic, and we know neither cause nor cure. The only recourse is research. Yet, as Cadman notes, the research productivity of young physician-investigators is threatened by pressure to support themselves by caring for patients and by their impaired opportunity to obtain grants, since renewal grants are four times more likely to be awarded than new ones.[3] Solutions may include developing a new national research strategy, providing more support (money and moral), and teaching the principles and practice of clinical investigation at all levels of medical training.

During this "meantime," what will become of academic medical centers? To serve our country's needs best, these centers must continue their teaching and research programs. Now, under managed care, the expense of treating patients can drain resources away from house staff education and continuing education. Funds are being shifted from investing in the future to protecting the present. Every incentive is away from caring for the most vulnerable, the most afflicted, the most needy. But if physicians in these centers do not provide care for sick patients and continue searching for clinical advances, who will? Will risk-adjusted payments come soon enough? Will they be adequate?

What is happening now to America's teaching institutions? A dangerous downward spiral seems to be swirling them into debility. There may be a subtle yet deadly falter in our education and research momentum. Newly minted health maintenance organizations (HMOs) and corporations determined to save money simply do not see teaching and research as their social responsibilities. No level of government is stepping in to help. As patients respond to the federal government policy of encouraging entry into Medicare HMOs, existing support of medical education drops. We, therefore, find with surprise and dismay that the future of our very foundation—teaching and research in academic medical centers—is at risk. Some have said that if economics continues eroding education, research, and the care of patients, there will be little left of medicine to reform by the time health care reform is under way.

Those who understand the risks our patients and their families face must insist that medical education and progress be high priorities. We simply must raise these issues to greater visibility. We cannot coast on past victories. Policymakers and the public may not appreciate the lag time between recognizing a problem, discovering a solution, and applying a new approach safely and effectively. They may not know that basic science, or the rain forest, may have clues that even precede recognition of a problem. To scale the peaks looming above us, we must recognize the need for the partnership of medical education and research, insist upon it, and form coalitions with our patients and others so we can pull and push each other along. We must use this "meantime" to work on a healthy future.

LINDA HAWES CLEVER, MD

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Perioperative Cardiac Morbidity—Epidemiology, Costs, Problems, and Solutions

THE REVIEW ARTICLE by Darryl K. Potyk, MD, in this issue of THE WESTERN JOURNAL OF MEDICINE addresses a timely and important subject.[1] Before discussing some of the issues brought up by Dr Potyk, I think it worthwhile to review the importance of the problem of perioperative cardiac morbidity.

Epidemiology

Cardiovascular disease continues to be the leading cause of death, accounting for one of every two deaths in the United States, Canada, Western Europe, and Japan.[2] Cardiovascular disease will continue to be a challenging problem over the next 50 years because of the acceleration in aging of the populations of these countries. The complications from cardiovascular disease are exacerbated by stress; thus, it is not surprising that cardiovascular disease complications are considerable in patients undergoing anesthesia and surgical intervention due to the stresses inherent in the prolonged perioperative period.

The impact of perioperative cardiac morbidity is substantial for patients undergoing either a cardiac or noncardiac operation, but I will discuss only those patients having a noncardiac operation. Of the 25 million patients per year in the United States who undergo a noncardiac operation, about a third, or 8 million patients, either have coronary artery disease, two or more major risk factors for coronary artery disease, or are older than 65 years.[3] Therefore, it is not surprising that when this large group of patients is subjected to stress over a three- to four-day perioperative period, cardiovascular complications result. The best estimates of serious perioperative cardiac morbidity—myocardial infarction, ventricular failure, unstable angina—range between 1% and 10% or more, depending on the subset of patients and the type of surgical procedure.[3] Overall, we estimate that about 4% of the 25 million patients, or more than 1 million patients, have serious perioperative cardiac morbidity following noncardiac surgical treatment in the United States.

The effects of aging on the surgical population are even more substantial than on the general population. Currently 25% of those having an operation (versus 10% of the general population) are older than 65, with 33% having cardiovascular disease.[2,3] Over the next 30 years, we estimate that 37 million patients a year will undergo an operation, with 12 million being older than 65 and 20 million having cardiovascular disease. As a result, perioperative cardiac morbidity also will increase substantially unless diagnostic and therapeutic techniques can be developed to mitigate the effects of the unrelenting process of aging.

Cost Estimates

Of the $900 billion annual United States health care cost, about $300 billion is spent on surgical cost (25 million operations per year times $12,000 per operation). Major adverse events following a surgical procedure constitute about 18% of the surgical cost, or $54 billion annually (United States).[4,5] Two thirds of this adverse-incident cost, or $33 billion, is attributable to cardiovascular complications following an operation, including myocardial infarction, ventricular failure, unstable angina, stroke, and cerebral dysfunction. The subgroup of cardiac complications costs about $22 billion, which is about 70% of the cost of cardiac complications in the medical population ($33 billion annually). In addition, because of the more rapid aging of patients being treated surgically, it is estimated that by 2018, surgical and medical cardiac complication costs will be nearly identical, each being $40 billion annually in the United States.[4,5]

Thus, perioperative cardiac morbidity is a serious and growing problem, affecting more than a million persons in the United States alone and consuming more than $20 billion annually in health care cost.

Solutions

The solution to the problem of perioperative cardiac morbidity has been addressed over the past 35 years, with most studies attempting to define the preoperative predictors of adverse events.[3] Defining such predictors, it was argued, enabled high-risk patient subsets to be identified, allowing the most effective medical therapy to be tried, alternate surgical techniques to be carried out, or the involved coronary arteries to be revascularized. The studies of the 1960s and 1970s did identify recent myocardial infarction as an important predictor, altering the standard of care. Pivotal studies of Goldman, Detsky, and others in the 1970s and 1980s extended the results of early studies and identified risk indices that allowed high-risk subsets to be ascertained.[3] More recently it has been recognized that the data from routine testing—history, physical examination, electrocardiogram, and chest x-ray film—may not be sufficiently sensitive, resulting in the investigation of more specialized testing. From these studies, performed during the 1980s and early 1990s, a series of recommendations evolved, suggesting that exercise stress testing, radionuclear assessment of ventricular function, ambulatory Holter monitoring, perfusion scintigraphy, or pharmacologic stress scintigraphy and echocardiography were sensitive and accurate tests that could be used for predicting results and therefore differentiating high-risk subsets.[6,7] Substantial controversy arose, however, for each of these modalities when other independent studies had contradictory results, suggesting that predictor values were not as high as those reported in the initial studies of these technologies.[8]

The recognition of this important problem of risk stratification and the examination of possibly important specialized tests, though yielding controversial results, led to the following important insights.

- No one preoperative test is accurate for predicting outcome when applied to a large spectrum of patients. Identifying a subset is critical.
- Perioperative myocardial infarction is a complex disorder, being precipitated by one or more mechanisms, including increases in myocardial oxygen consumption, precipitating ischemia and infarction; increases in the coagulable state, precipitating thrombosis; and other mechanisms, including altered vascular tone, endothelial function, and leukocyte function.[3] As a result, a preoperative test that alters myocardial oxygen consumption, such as exercise treadmill or dobutamine-stress scintigraphy, perhaps will only predict infarctions induced by similar abnormal changes—oxygen consumption increases—but will not predict infarctions associated with a different mechanism, such as thrombosis. Similarly, a test that al-

ters coronary artery tone, such as dipyridamole-thallium scintigraphy, may only predict infarctions associated with altered tone or coronary steal and not infarctions precipitated by increases in oxygen consumption, for example.[8,9] Therefore, the reasons for the limitations of these tests are understandable.

• Recently it has been appreciated that it is not only preoperative chronic disease that affects outcome, but also intraoperative and postoperative pathologic changes, such as the stress response, alterations in hemodynamics, or coagulation changes.[6] Thus, preoperative testing is inherently limited, and preoperative information, though important, should be used in association with information derived from perioperative physiologic changes to comprehensively define the predictors of outcome. For example, a patient may have a stable preoperative disease, but may be subjected to intensive intraoperative or postoperative stresses and therefore be converted, in effect, to a high-risk patient. Similarly, a patient who is at risk preoperatively, manifesting either a high risk-index score, ischemia, or a redistribution abnormality, may undergo a relatively benign intraoperative and postoperative course and be at little risk for an adverse cardiac event.

Therefore, preoperative testing is important for distinguishing high-risk subsets; however, information derived from such testing must be evaluated along with other intraoperative and postoperative "stress testing results" or perturbations.

Risk Assessment and Vascular Surgery

Dr Potyk addresses cardiac risk assessment in the population of patients undergoing peripheral vascular surgery.[1] The focus on patients having this type of operation is appropriate because such patients represent a high-risk subset with cardiac complications occurring with a frequency of 5% to 20% in reported studies. This is also the group in whom specialized preoperative cardiac testing has been investigated most extensively. In the first section, the relationship between coronary artery disease and peripheral vascular disease is reviewed, allowing insight into the critical underlying problem. The second section addresses cardiac risk assessment using noninvasive cardiac testing. Several of the controversies given in the discussion earlier are highlighted and indexed, including a number of the key papers. Limitations of several of these techniques also are addressed. Because of the considerations regarding the complexity of the abnormal changes leading to perioperative infarction and the considerations regarding the importance of the preoperative existence of chronic disease versus intraoperative and postoperative stress responses, many of the noninvasive tests are limited when applied to the general population or even to subsets of high-risk patients.

The third section addresses preoperative strategies to decrease the incidence of postoperative complications. Although the literature on coronary artery bypass grafting and percutaneous transluminal coronary angioplasty generally is supportive, Potyk raises considerations regarding cumulative morbidity and mortality, when considering prophylactic revascularization before surgery. Furthermore, conclusions regarding such strategies remain speculative because of the absence of large-scale multicenter outcome studies. Finally, Potyk emphasizes the importance of intraoperative monitoring techniques; few prospective large-scale studies address such technology, however. In fact, recent studies may even suggest that the widespread use of sensitive techniques such as intraoperative transesophageal echocardiography may not be indicated in a broad spectrum of patients.[10] A cautious approach is warranted when interpreting these promising early studies. The importance of the postoperative period is appropriately emphasized; it is now recognized that the majority of infarcts occur not intraoperatively, when stress is presumably highest, but postoperatively. This finding confirms the importance of modulating stress by intraoperative anesthetic and stress-modulating techniques, and it challenges us to develop similar stress-modulating therapies (such as the analgesics, sedative hypnotics, or α_2-agonists) and anti-ischemic therapies (such as adenosine-regulating agents) for this important period.

Conclusions

Perioperative cardiac morbidity is now recognized as a substantial, challenging, and costly problem. The solution to this problem involves preoperative subset identification using cost-effective, specialized testing techniques that have been proved in large-scale outcome trials. Equally critical to the solution, however, is the development of intraoperative and postoperative detection techniques and therapeutic modalities, validated in rigorous large-scale outcome trials. The mandate is clear—we must take an aggressive approach to mitigate cardiac morbidity and mortality in aging high-risk surgical patients.

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Bilateral Psoas Abscesses Following Acupuncture

To the Editor: We report a case of bilateral psoas abscesses, treated by percutaneous drainage and prolonged antibiotic therapy, in which an acupuncture procedure was a possible cause.

Report of a Case

The patient, a 49-year-old man with a history of chronic low back pain, presented with acute right lower quadrant abdominal pain, nausea, and vomiting. Over the previous two weeks, he had experienced malaise, anorexia, night sweats, bilateral leg edema, and a 6-kg (13-lb) weight loss. Three weeks before admission, he underwent acupuncture of both sides of his lower back. The procedure was done by a licensed, United States-trained acupuncturist who used disposable needles after "prepping the area" with rubbing alcohol.

On physical examination, he was pale, appeared ill, and had a temperature of 39°C, pulse 110 beats per minute, respirations 20 per minute, and blood pressure 150/70 mm of mercury. Other abnormal findings were diffuse abdominal tenderness with a fullness in the right lower quadrant and pronounced bilateral pitting edema. Relevant laboratory findings included a leukocyte count of 33.1×10^9 per liter (0.71 neutrophils, 0.21 bands, 0.08 lymphocytes), hematocrit of 0.3 (30%), total protein level of 60 grams per liter (6 grams per dl), and an albumin value of 29 grams per liter (2.9 grams per dl). The erythrocyte sedimentation rate was normal.

A bone scan showed no osteomyelitis. Computed tomography (CT) of the abdomen showed generalized enlargement of both psoas muscles with mixed areas of attenuation (Figure 1). Fine-needle aspiration of these areas yielded pus that grew *Staphylococcus aureus*. The abscesses were drained percutaneously under CT guidance. The patient received nafcillin sodium intravenously for six weeks and then oral dicloxacillin for six weeks. Six months after treatment, clinical evaluation and CT showed complete resolution.

Psoas abscesses should be suspected in patients with fever, abdominal pain, and a limp. Classic signs include flexion plus external rotation of the hip and a palpable mass in the lower abdominal quadrants. Associated findings are leukocytosis, anemia, and an increased erythrocyte sedimentation rate. Computed tomography or ultrasonography suggests the diagnosis, but aspiration or biopsy is needed for confirmation. Treatment includes external drainage and antibiotic therapy. Bilateral psoas abscesses are uncommon, with fewer than 500 cases reported in the literature.[1] Secondary abscesses result from the direct extension of an inflammatory process (such as Crohn's disease or vertebral osteomyelitis). Primary abscesses do not have a defined cause; it has been proposed that previous trauma, gross or microscopic, is required for their development. *Staphylococcus aureus* is the single most common pathogen in these cases. Our literature review elicited only one case in which the development of a psoas abscess was presumed to be caused by a medical intervention. A right psoas abscess developed after the patient received anesthetic blockades in the lumbogluteal region.[2]

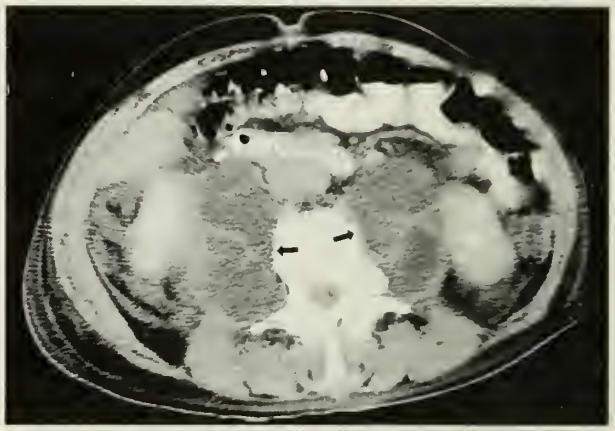

Figure 1.—An abdominal computed tomographic scan shows bilateral psoas abscesses (**arrows**).

Acupuncture is considered to be a safe procedure without major complications. Life-threatening complications have occasionally been described, such as pneumothorax.[3] Infectious complications, such as transmission of the human immunodeficiency virus, have also been reported.[4] In this case, the temporal association between the use of acupuncture and the development of symptoms suggests an unusual origin of these bilateral psoas abscesses.

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Breast Implants and Autoimmunity

To the Editor: While the controversy over breast implants and immunity rages on, I am interested in the apparent failure to consider what I view as a fundamental issue: breast implants are not distributed randomly in women. They are given to women who have selected themselves—certainly by morphology, and possibly also

by psychology. Yet, as in the recent article by Claman and Robertson,[1] studies on this subject often seem to proceed on the assumption that women with and without breast implants are otherwise equivalent except for this issue. The authors compared the occurrence of antinuclear antibodies in women with and without breast implants. No attempt seems to have been made to determine if these subgroups were the same before the surgical procedure.

Workers throughout the emerging field of psychoneuroimmunology argue that behavioral state may influence immune function. And articles regarding depression and immune dysregulation point out the relevance of the behavioral state to standard clinical disease.[2] Might this be important in the immune studies done on women with breast implants? Are we to assume that women who see themselves as needing physical modification are of the same psychological makeup as women who do not?

Genetics also has long been accepted as a fundamental issue in autoimmune disease. Yet, if we ignore this in the breast implant arena, we are left with the assumption that women who choose breast implants bear the same genetic substrate as women who do not.

In recent decades young women have recurrently predominated in furors over several poorly defined, chronic syndromes, including those of chronic fatigue (alternatively, Epstein-Barr virus), fibromyalgia, chronic candida, chronic whiplash, thoracic outlet, and others. These syndromes share the recurrent demographics of young women with long-term subjective symptoms bearing marginal correlation to laboratory factors. Of these syndromes, the first three bear witness to the recurrent question regarding some underlying immune dysfunction. The Epstein-Barr virus syndrome is especially pertinent for its historical and evolutionary perspectives. How many more incarnations of this issue must we have before we start recognizing the similarities of this recurrent story?

It remains to be determined whether the breast implant furor will turn out to reveal a biologic issue or another incarnation of a sociologic issue. Or, as in the case of some of the syndromes mentioned, we might discover a mixture: a molehill of pathology flourishing in a mountain of symptoms under the influence of social expediency. If we are to accurately answer the immunologic question, we must understand both the silicone and its recipient.

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* * *

To the Editor: The article "Antinuclear Antibodies and Breast Implants" by Claman and Robertson is very provocative, suggesting the possibility of an autoimmune problem related to breast implants.

To better assess the situation, however, one needs to know the incidence of antinuclear antibodies on Hep-II cells in a group of women who had "various symptoms" (group II) who had *no* implants. The same is true for women who have an autoimmune disease but do *not* have implants.

The question we are really asking is whether or not there is an increase in antinuclear antibodies in patients because of an implant. Because other diseases may cause antinuclear antibodies to be present, the denominator needs to be known.

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* * *

Dr Claman Responds

To the Editor: Perhaps the most interesting result in our study is that women with breast implants who feel well have a higher than expected prevalence of positive antinuclear antibody (ANA) tests. Dr Barbuto points out that women who seek breast implants (most often for augmentation) differ psychologically from those who do not. This is true and has been documented. He also points out that there is literature indicating that the behavioral state may influence immune function. To our knowledge, however, there are no data to indicate that behavioral states by themselves influence ANA positivity. It would be nice to have psychological profiles of our patients and controls before surgery, as suggested by Dr Barbuto. This is not possible with our patients, however, as the implants were put in as long as 25 years ago. For a new prospective study, it would be useful to have both screening psychological profiles and baseline ANA tests, although it is easy to see both practical and theoretical problems in trying to get these studies done. With regard to genetic influences, we agree that they are important. We are HLA-typing the next cohort of patients and controls.

Dr Koons makes a good point: we did not include ANA data from control women comparable to our group II—women with fatigue, arthralgias, and myalgias but no implants. We omitted these women, but not because we did not try to find them. We have had promises from private rheumatology clinics and a large general practice clinic—promises but virtually no referrals, particularly of women with those symptoms without a previous ANA test. We are now trying the newspapers.

Because we lacked this control group, we did not emphasize the prevalence of positive ANA tests in the women in group II. We cited an article that found a prevalence of 9% positive ANA tests in patients with fibromyalgia. We also have additional data of our own (run in a different ANA laboratory) showing a prevalence of 12% positive ANA tests in women with diagnosed fibromyalgia. What is far more interesting is the 18% prevalence of ANAs in group I—asymptomatic but with implants—compared with their appropriate asymptomatic

control group 0 without implants, which had 0% positive ANA tests.

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Previous Donner Party Research

To THE EDITOR: The conclusions concerning Donner Party mortality presented by S. A. McCurdy in this journal[1] merely restate those that I presented in an article published in a major anthropological journal four years ago.[2] My article went uncited by McCurdy even though the results of my work have been discussed by such authors as Shipman[3] and Diamond[4] in widely distributed sources and were restated in my recent book on the history of the Great Basin.[5]

Even a passing effort by McCurdy to discover previous work in this area would have revealed my paper as well as those by Shipman and Diamond. For instance, it took me less than a minute to find the Grayson and Diamond references by searching under "Donner Party" in the Online Computer Library Center (OCLC) catalogue. It is unfortunate that McCurdy made no effort to discover whether he was merely repeating the work of others and that he gave no credit to those who came before him. As a result, he gave the impression of producing novel results when, in fact, he had not. It is equally unfortunate that THE WESTERN JOURNAL OF MEDICINE did not choose reviewers who might be expected to be familiar with research in this area.

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* * *

Dr McCurdy Responds

To THE EDITOR: I appreciate the opportunity to acknowledge Dr Grayson's previous work[1] regarding the Donner Party, and I regret not having learned of it in time to cite it in my recently published article.[2] In preparing the manuscript, I read historical texts on the episode and conducted a MEDLINE search of the biomedical database back to 1966. Unfortunately, the anthropological research journal in which Grayson published was not indexed in this database. Nor were the secondary sources he mentions. In the year preceding its publication, I shared drafts of the manuscript and discussed the work with colleagues and interested persons, presented it at the national American Public Health Association meeting, and finally submitted it for formal peer review. None of this brought his article to my attention. When I learned of his work shortly before release of my article, I called out of courtesy to let him know that it would be forthcoming and that I was sorry not to have known of his work in time to cite him.

Grayson and I both examined demographic characteristics of the Donner Party and their influence on mortality, but salient differences in approach, methods, and findings exist between our studies. He showed that persons dying were more likely than survivors to be old or very young, male, and to have smaller kin groups. This descriptive approach did not allow a quantitative comparison of these factors for their relative importance or effect on mortality.

My work is new in bringing an analytic and epidemiologic focus on quantitative assessment of risk factors. Multivariate regression techniques yielded relative risks for mortality that were adjusted for known cofactors, allowing comparison with respect to the strength of their independent effects. For example, the analysis shows in quantitative terms the preponderant effect of age (relative risk of 6.6 for those younger than 6 years and a relative risk of 8.4 for those 35 years of age or older). The comparatively weaker effects of male sex and traveling without other family members (each with a relative risk of 2.0) are also shown. Our findings also differ with respect to the effect of family size on survival. No independent effect of family size per se is evident after restricting analysis to persons traveling with at least one other family member. In keeping with the epidemiologic focus, I also noted possible implications for medical responses to starvation disasters. Age and sex identify high-risk groups and are immutable factors. In contrast, family networks may be affected by response efforts, which could influence survival rates.

I hope readers of the journal will find this epidemiologic analysis useful and interesting despite the unintentional omission in not crediting Grayson's previous work.

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

The Art of Sitting

LEON MORGENSTERN, MD, *Los Angeles, California*

"She's cantankerous. I doubt that she'll talk to us," the chief resident said apologetically.

Such was my introduction to Mrs G, the patient in room 7817. The rule on my scheduled teaching rounds was that all patients should be forewarned of the visit, lest they be frightened by an awesome assemblage of strangers in white. Mrs G was unhappy with her nurses, her food, her physicians, and probably herself. She had responded with apathy, if not outright displeasure, to the idea of being introduced to the attending physician.

"Well, let's try anyway," I suggested. "Perhaps we can find out why she's so negative."

As we entered, Mrs G eyed us suspiciously, and her glances darted impatiently from face to face. She responded stiffly to the introduction and to my greeting. But I quickly spotted my opportunity. It was the empty chair at her bedside, which I occupied.

My sitting down took Mrs G by surprise, and I detected a softening of her glance as we began to engage, unhurriedly, in some small talk irrelevant to her illness. Gradually we worked into the details of her complaints, and slowly her whole demeanor changed. She began to talk animatedly, punctuating her story with smiles and expressions of friendliness. She knew we were interested. Slowly the details of her illness emerged. When we left, the lesson of Mrs G's illness was secondary, I thought, to the lesson I had been able to transmit on the "art of sitting."

During many years of practice, I had witnessed countless flying visits by both house staff and attending physicians, alone or in concert. Standing by the edge of the bed or towering over the patient at bedside, encounters were short, polite, and often perfunctory. The importance of the visit was eclipsed by the pressures of time and tasks undone. Yet, for the patient this was the event of the day—the doctor's visit is unmatched in importance by anything else that occurs before or after.

To avoid the effects of the flying visit, I have promulgated my own set of rules on the art of sitting with a patient:

- Sit.
- Sit close.
- Sit patiently.
- Sit interestedly.
- Look at the patient, not at the chart.
- Do not sit on the bed.
- Sit long enough, but not too long.
- When leaving, offer your hand and some words of warm encouragement and praise. Touch is also therapeutic.

There are ancient Jewish laws for visiting the sick, as codified in the *Schulchan Aruch* by Joseph Karo in the Middle Ages. Among them is the rule for sitting: "He who visits the sick should sit in front of the ailing person, neither above or below him. . . ." The implication is that sitting sends a message of concern and caring.

I was grateful to Mrs G for letting me demonstrate the art of sitting. Future visits with this not-so-cantankerous patient would not be so difficult.

(Morgenstern L: The art of sitting. West J Med 1994; 161:93)

From the Department of Surgery, Cedars-Sinai Medical Center and UCLA School of Medicine, Los Angeles, California.
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Lessons From the Practice

The Right to Choose

THEODORE B. SCHWARTZ, MD, *Boise, Idaho*

It happened some 30 years ago, long before today's lacerating conflict between pro-life and pro-choice forces, but, still, this lesson remains indelibly imprinted in my mind. A young woman with diabetes mellitus had been under my care for about a year. While I can no longer remember the specific details related to her status, I can picture her person clearly. Mary was a pretty, round-faced blonde with a glowing complexion. She had been married recently to an adoring, indulgent husband. The diabetes had appeared in childhood, and despite moderately good control, Mary's blood pressure was beginning to rise.

Mary was eager to become pregnant. Uneasy, I told her that it was not a great idea, pointing out the substantial risks to mother and child. In those days maternal mortality approached 5%, and fetal loss was 30% to 40%; the benefits of meticulous control of glucose levels during pregnancy had not yet been documented. Mary, a devout Catholic, listened but remained noncommittal.

Several months later she reappeared, radiant with the news of her pregnancy. I worried, but agreed to follow her course closely. I told her bluntly that this should be her only child because future pregnancies would be too hazardous.

Things did not go well. Mary's blood pressure began to rise, and soon I could see small, wormy new blood vessels appear in her fundi. I told her of the threat of blindness and added that if her status should continue to deteriorate, a therapeutic abortion would have to be considered. Mary, still in optimistic good humor, assured me that all would work out satisfactorily.

The retinopathy accelerated rapidly with the appearance of hemorrhages bilaterally, and she became definitely hypertensive.

It was time for decisive action, I thought. I met with Mary and her husband and explained, sympathetically but firmly, that the pregnancy now posed an unacceptable danger to her health. It would have to be terminated. Mary responded calmly that she could not tolerate the idea of an abortion and that she would willingly accept any risk to carry her 10-week-old fetus to term. The following interchange—or something like it—then ensued:

T.B.S., with tense formality: "Mary, we have a big problem. Just as your convictions will not permit you to have an abortion, mine will not permit me to stand by and watch you go blind and your health deteriorate. If you insist on going ahead with the pregnancy, I cannot, in good conscience, continue to be responsible for your care. I will, of course, see to it that your records are transferred to any physician you choose."

Mary, white-faced with controlled anger: "No, Dr Schwartz, I am not going to have an abortion, and you are not going to send me to another doctor. You are my doctor; you've taken good care of me. I trust you, and you'll just have to continue to do the best you can."

Dumbfounded, I sat for a time, absorbing her outburst and contemplating where my duty lay. It became clear that hers was, in an inversion of today's parlance, an "informed denial" and that her right to choose superseded my own. Even more distressing was the awareness that, arrogantly, I had attempted to use my lofty scruples as a weapon to pressure my patient into compliance, and, by doing so, I had forfeited my claim to rectitude.

Mary succeeded in carrying the fetus to term, but she delivered a stillborn baby. She also became totally blind. The last time I ushered her into my office, she greeted me with that same enduring, beatific smile. Despite all the travail, she knew she had made the right choice, and I learned early on that an informed patient has the right to choose.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Schwartz TB: The right to choose. West J Med 1994; 161:94)

From the Departments of Medicine, University of Washington School of Medicine, Seattle, and Rush Medical College, Chicago, Illinois.
Reprint requests to Theodore B. Schwartz, MD, 4820 Roberts Rd, Boise, ID 83705.

Poems

CONSCIOUS SEDATION

She says
she doesn't want
to remember
anything.
Young, anxious,
she will be hard
to sedate,
will rise up against
the cloak of numbness.
She will not
trust me
enough.

So I laugh
about the "joy juice"
I will push
through her veins—and I do it,
not slow, but
twice as fast.
She says the room
just moved down
and I say—
"It's the medicine."
A smile, then
it fades, she falls
not to rest but beyond,
to the place where
anxiety is
and then she bubbles
back, "My feet
are hazy."
I say, "It's
the medicine"—a
smile, a fade,
a bouncing back; "I don't want
to be here when I'm here . . .

. . . if you know what I mean."

More valium,
more demerol,
she doesn't speak
now
but her heart quickens
against the fog
and I know
when I touch her
she will rise up
so I wait
until the mantle is heavy
and smothers even
the quick breath of fear

and I can begin.

DAVID WATTS, MD©
Mill Valley, California

* * *

DREAM ANALYSIS

Hair plastered by sweat onto the dreamer's face,
You lead me down the path of righteousness for your name's sake,
For the sake of the dream.
I wake and search the sweet darkness, rapidly receding,
For signs of how to live my daylight life.
My plans are frivolous, lighter-than-air,
They float away and disappear.
I need your dark ballast.
The adding and subtracting, dividing and multiplying,
Calculating the cost, the angle, the gimmick,
Leaves me as weak as water.
You divine the heart of the matter while I sleep,
Without formulae or logic,
So, I wait for your measure of wisdom.

DENISE L. DAVIS, MD©
Oakland, California

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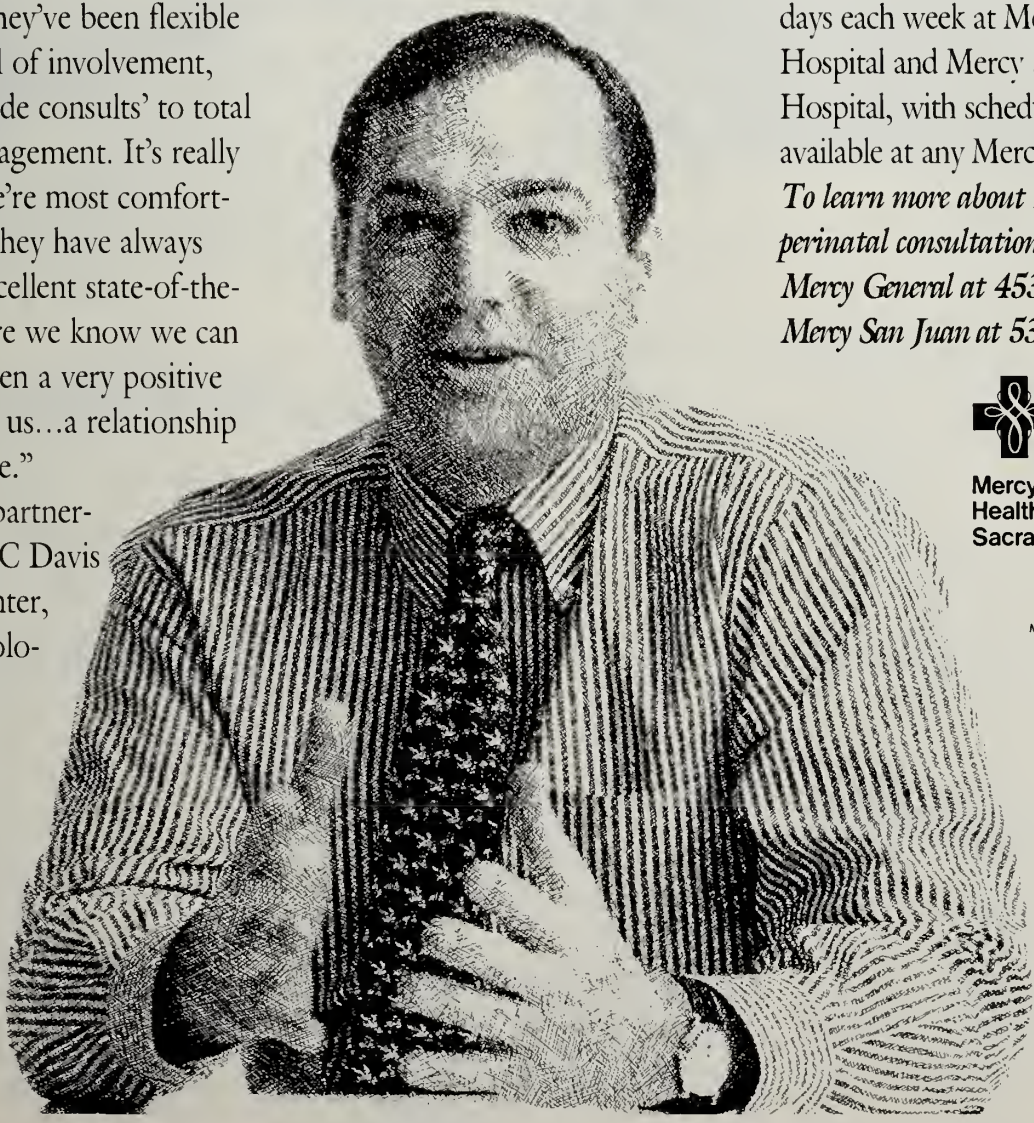

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(Continued from Page 25)

October 15—**Interventional Radiology.** Seattle. Sat. Contact: U/W.

October 27-30—**7th Annual Pediatric Critical Care Colloquium.** Seattle. Thurs-Sun. Contact: Children's, (206) 526-2501.

October 28-29—**Mental Health Update.** Seattle. Fri-Sat. Contact: U/W.

November 3-4—**Current Concepts in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 4—**Muscular Dystrophy and Related Disorders.** Seattle. Fri. Contact: Children's, (206) 526-2501.

November 11-12—**Pediatric Advanced Life Support.** Seattle. Fri-Sat. Contact: Children's, (206) 368-4802.

December 2—**Pediatric Update.** Seattle. Fri. Contact: Children's, (206) 526-2501.

December 8-10—**10th Annual Infectious Disease Conference.** Seattle. Thurs-Sat. Contact: Pacific Northwest Medical Education Institute, (206) 261-2160.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

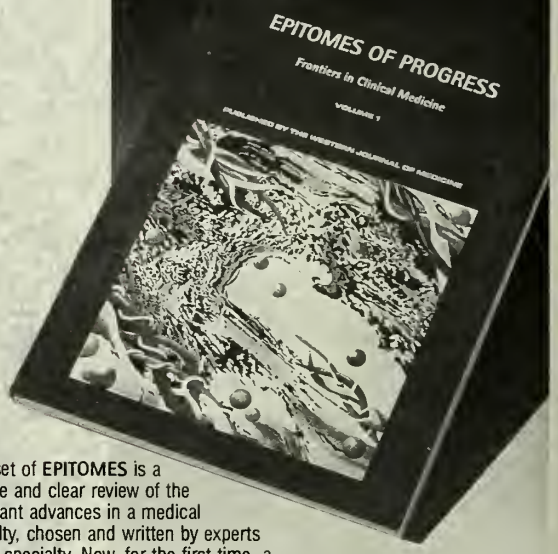
PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762. ◆

epitome i-'pit-ə-mē\ *n* [L, fr. Gk *epitomē*, fr. *epitemnein* to cut short, fr. *epi-* + *temnein* to cut — more at TOME] (1520) **1 a :** a summary of a written work **b :** a brief presentation or statement of something **2 :** a typical or ideal example: EMBODIMENT (the British monarchy itself is the ~ of tradition —Richard Joseph) **3 :** Plural — *Epit-o-mes* — A regular FEATURE of *The Western Journal of Medicine,* now available in a single, bound volume.



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(Continued on Page 100)

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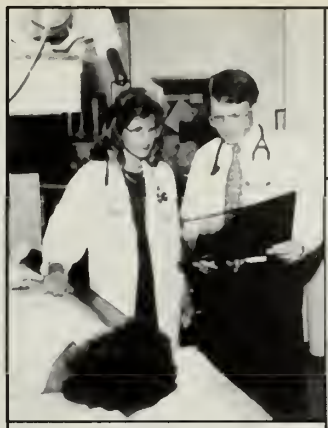

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(Continued on Page 103)

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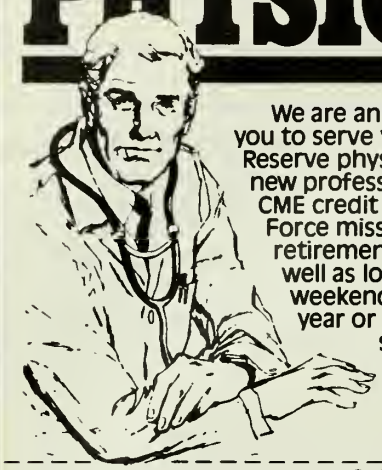

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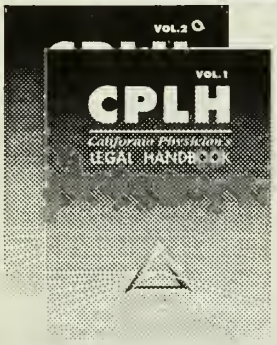

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Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 7-9, 1994, Ritz-Carlton Maunalani, Hawaii.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 28-30, 1994, Sun Valley.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 29-October 1, 1994, Holiday Inn, Great Falls.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 27-30, 1995, Resort at Squaw Creek, 1995.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. May 12-13, 1995, Albuquerque.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 21-24, 1994, University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 22-24, 1994, Wenatchee.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 8-10, 1995, Jackson Lake Lodge, Moran.

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REFERENCES:

1. Britton JW, Fajardo JE, Krafte-Jacobs B. Clinical and laboratory observations. Comparison of mupirocin and erythromycin in the treatment of impetigo. *J Pediatr.* 1990;117:827-829.
2. *Bactroban* prescribing information.
3. McLinn S. A bacteriologically controlled, randomized study comparing the efficacy of 2% mupirocin ointment (Bactroban) with oral erythromycin in the treatment of patients with impetigo. *J Am Acad Dermatol.* 1990;22:883-885.
4. Rice TD, Duggan AK, DeAngelis C. Cost-effectiveness of erythromycin versus mupirocin for the treatment of impetigo in children. *Pediatrics.* 1992;89:210-214.

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DESCRIPTION

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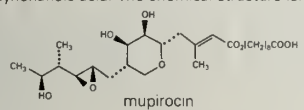

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Application of ^{14}C-labeled mupirocin ointment to the lower arm of normal male subjects followed by occlusion for 24 hours showed no measurable systemic absorption (<1.1 nanogram mupirocin per milliliter of whole blood). Measurable radioactivity was present in the stratum corneum of these subjects 72 hours after application.

Microbiology: The following bacteria are susceptible to the action of mupirocin *in vitro*: the aerobic isolates of *Staphylococcus aureus* (including methicillin-resistant and β-lactamase producing strains), *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, and *Streptococcus pyogenes*.

Only the organisms listed in the INDICATIONS AND USAGE section have been shown to be clinically susceptible to mupirocin.

INDICATIONS AND USAGE

Bactroban (mupirocin) Ointment is indicated for the topical treatment of impetigo due to: *Staphylococcus aureus*, beta-hemolytic *Streptococcus**, and *Streptococcus pyogenes*.

*Efficacy for this organism in this organ system was studied in fewer than ten infections.

CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components.

WARNINGS

Bactroban Ointment is not for ophthalmic use.

PRECAUTIONS

If a reaction suggesting sensitivity or chemical irritation should occur with the use of *Bactroban* Ointment, treatment should be discontinued and appropriate alternative therapy for the infection instituted.

As with other antibacterial products prolonged use may result in overgrowth of nonsusceptible organisms, including fungi.

Bactroban is not formulated for use on mucosal surfaces. Intranasal use has been associated with isolated reports of stinging and drying.

Polyethylene glycol can be absorbed from open wounds and damaged skin and is excreted by the kidneys. In common with other polyethylene glycol-based ointments, *Bactroban* should not be used in conditions where absorption of large quantities of polyethylene glycol is possible, especially if there is evidence of moderate or severe renal impairment.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at systemic doses, i.e., orally, subcutaneously, and intramuscularly, up to 100 times the human topical dose and have revealed no evidence of impaired fertility or harm to the fetus due to mupirocin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether *Bactroban* is present in breast milk. Nursing should be temporarily discontinued while using *Bactroban*.

ADVERSE REACTIONS

The following local adverse reactions have been reported in connection with the use of *Bactroban* Ointment: burning, stinging, or pain in 1.5% of patients; itching in 1% of patients; rash, nausea, erythema, dry skin, tenderness, swelling, contact dermatitis, and increased exudate in less than 1% of patients.

DOSAGE AND ADMINISTRATION

A small amount of *Bactroban* Ointment should be applied to the affected area three times daily. The area treated may be covered with a gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.

HOW SUPPLIED

Bactroban (mupirocin) Ointment 2% is supplied in 1 gram Single Unit Packages of 50 and in 15 gram and 30 gram tubes.

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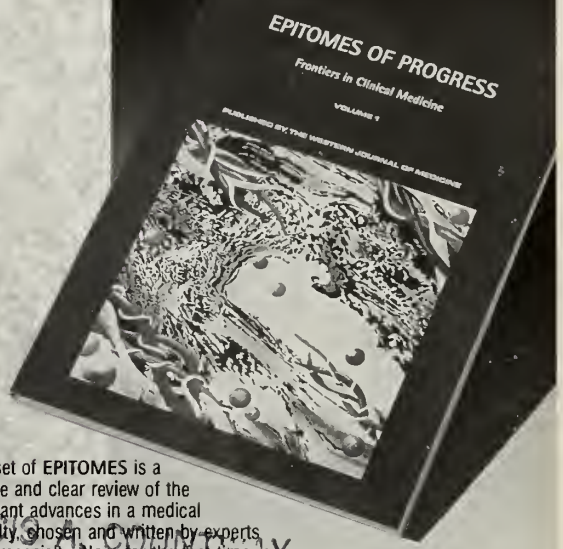
epitome i-'pit-ə-mē\ *n* [L, fr. Gk *epitomē*, fr. *epitemnein* to cut short, fr. *epi-* + *temnein* to cut — more at TOME] (1520) **1 a** : a summary of a written work **b** : a brief presentation or statement of something **2** : a typical or ideal example: EMBODIMENT (the British monarchy itself is the ~ of tradition —Richard Joseph) **3** : Plural — *Epit-o-mes* — A regular FEATURE of *The Western Journal of Medicine*, now available in a single, bound volume.



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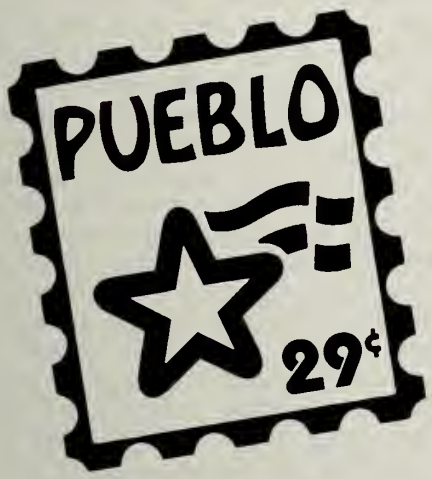

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2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press 1966, pp 35-51 [author of book is same as author of chapter]

4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Edition. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 [authors of book differ from chapter author]

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DANIEL BLUESTEIN, MD, and M. ELIZABETH STARLING, MS, LPC

From the Department of Family and Community Medicine, Eastern Virginia Medical School, Norfolk, Virginia, and Highland Hall Hospital, Ashville, North Carolina.

144 **Improving Cross-cultural Skills of Medical Students Through Medical School-Community Partnerships**

LOIS MARGARET NORA, MD, JD; STEVEN R. DAUGHERTY, PhD; AMY MATTIS-PETERSON; LINDA STEVENSON; and LARRY J. GOODMAN, MD

From Rush Medical College and Hispanic Health Alliance, Chicago, Illinois, and Center for Global Education in Cuernavaca, Augsburg College, Minneapolis, Minnesota.

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MICHAEL C. PETERSON, MD

From the Department of Medicine, LDS Hospital, Salt Lake City, Utah.

153 **Lead Poisoning**

PHILIP J. LANDRIGAN, MD, MSc, and ANDREW C. TODD, PhD

From the Department of Community Medicine, Mount Sinai School of Medicine, New York, New York.

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VIVIAN M. DICKERSON, MD

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H. TRENT MacKAY, MD, MPH, and MARY L. KAMB, MD, MPH

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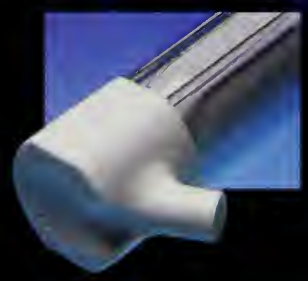
QD STAYING POWER

Positron emission tomography (PET) image of ^{11}C-triamcinolone acetonide following intranasal administration of Nasacort[1]



ONCE DAILY

Nasacort®

(triamcinolone acetonide) Nasal Inhaler

Provides comfortable, prompt relief of allergic rhinitis and effective QD dosing

- Nasacort remains in the nasal mucosa with no measurable effect on HPA function [1-3]*

  Duration of acquisition of the PET image was approximately 55 minutes due to ^{11}C decay ($t_{1/2}$ of 20 minutes).[1] (n=2)

- Nasacort provides prompt relief for many patients — symptom reduction may occur as soon as 24 hours after starting therapy [4]
- Nasacort provides effective QD dosing — 2 puffs/nostril/day effectively controls symptoms in most patients; however, QD dosing can be increased to 4 puffs/nostril/day when necessary

Please see brief summary of prescribing information on adjacent page.

* In doses up to 440 mcg day.[3]

Nasacort...Once Is Enough

ONCE DAILY
Nasacort® Nasal Inhaler
(triamcinolone acetonide)

For Intranasal Use Only
Shake Well Before Using

BRIEF SUMMARY

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

The use of Nasacort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Nasacort Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

PRECAUTIONS

General: In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local therapy and discontinuance of treatment with Nasacort Nasal Inhaler.

Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. Nasacort at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see CLINICAL TRIALS section).

Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances.

When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasacort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients being treated with Nasacort Nasal Inhaler should receive the following information and instructions.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Patients should use Nasacort Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations.

Carcinogenesis, Mutagenesis: Animal studies of triamcinolone acetonide to test its carcinogenic potential are underway.

Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m^2/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m^2/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m^2/day or 110 mcg/m^2/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery. Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5 - 15.0 mcg/kg/day or 20 - 110 mcg/m^2/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m^2/day and 7.0 mcg/m^2/day).

Pregnancy: Pregnancy Category C. Like other corticoids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m^2/day in the rat and 320, 640 and 1280 mcg/m^2/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m^2/day). The doses of 0.02, 0.04, 0.08, and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51, and 318.7 times the minimum recommended dose of 110 mcg of Nasacort per day and 3.2, 6.4, 12.7, and 80 times the maximum recommended dose of 440 mcg of Nasacort per day based on a patient body weight of 70 kg. Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Nasacort Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in children below the age of 12. Oral corticoids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS: In controlled and uncontrolled studies, 1257 patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed Nasacort canister. These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days).

The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received Nasacort. Nasal irritation was reported by 2.8% of the patients receiving Nasacort. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received Nasacort and included: dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects.

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).

OVERDOSAGE: Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects if the nasal application of the 15 mg of triamcinolone acetonide was administered all at once.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Please see product circular for full prescribing information.

REFERENCES:

1. Data on file. Rhône-Poulenc Rorer Pharmaceuticals Inc. **2.** Ziemniak JA: Pharmacokinetics of intranasal triamcinolone acetonide. *J Respir Dis* 1991;12 (3, Suppl):S41-S42. **3.** Feiss G, Morris R, Rom D, et al: A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function. *J Allergy Clin Immunol* 1992;89:1151-1156. **4.** Findlay S, Huber F, Garcia J, et al: Efficacy of once-a-day intranasal administration of triamcinolone acetonide in patients with seasonal allergic rhinitis. *Ann Allergy* 1992;68(3):228-232.

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ABSTRACTS AUGUST 1994

(Wiktor SZ, Gallaher MM, Baron RC, Watson ME, Sewell CM: Firearms in New Mexico. West J Med 1994; 161:137-139)

To determine the prevalence of firearm ownership and storage practices in New Mexico, we did a random-digit-dialing survey of New Mexico residents in October 1991. Of 200 households surveyed, 79 (40%) had 1 or more firearms in the home. Rural households were more likely than urban households to have firearms (44% versus 30%), and households with annual incomes of greater than $25,000 were more likely to have a firearm than households with incomes of $25,000 or less (41% versus 33%). Household firearm ownership did not vary with the presence of young (<15 years old) children (38% with children versus 41% without). Handguns were generally owned for self-protection, and rifles were owned for hunting. Of households with firearms, 24% stored them unsafely (unlocked and loaded or unloaded but with ammunition nearby), including 21% of households with young children. Of the households with handguns only, 40% stored these firearms unsafely compared with 13% of those with rifles only. The prevalence of gun ownership in New Mexico is similar to that reported in national surveys; handguns are stored less safely than rifles; and the presence of young children in the home does not appear to improve firearm storage safety.

FIREARMS **HANDGUNS**
GUN OWNERSHIP **FIREARM DEATHS**

(Wiktor SZ, Gallaher MM, Baron RC, Watson ME, Sewell CM: Firearms in New Mexico. West J Med 1994; 161:137-139)

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FIREARMS **HANDGUNS**
GUN OWNERSHIP **FIREARM DEATHS**

Three copies of this abstract are provided to help you in filing and cross-referencing research articles.

Continuing Medical Education

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

September 10-11—**5th Annual Pulmonary and Infectious Diseases Seminar: September in Sedona.** Mayo Clinic-Scottsdale at Los Abrigados Resort, Sedona. Sat-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

September 25-29—**44th Annual Southwest OB/GYN Meeting.** Southwest OB/GYN Society at Loews Ventana Canyon Resort, Tucson. Sun-Thurs. Contact: Jay Epstein, MD, (602) 678-1111.

October 7-8—**Clinical Assessment in Today's World of Medicine for Nurses.** Mayo Clinic-Scottsdale at Ashton B. Taylor Auditorium, Scottsdale. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

October 8—**Audiology Videoconference.** Mayo Clinic-Scottsdale. Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

October 14-15—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Doubletree Hotel, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

October 21-22—**Parkinson's Disease and Movement Disorders for the Practitioner.** Mayo Clinic-Scottsdale at Ritz-Carlton Hotel, Phoenix. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

October 28-30—**Arrthymias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Camelback Inn, Scottsdale. Fri-Sun. Contact: Karen DeBont, (800) 421-3756.

November 3-6—**24th Annual Meeting: Musculoskeletal & MRI.** Maricopa Medical Center, Department of Radiology, at Camelback Inn, Scottsdale. Thurs-Sat. Contact: (602) 267-5366.

November 4-5—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

November 4-5—**Hematology and Oncology for Primary Care Physicians.** Mayo Clinic-Scottsdale at the Orange Tree Golf Resort, Scottsdale. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

November 7-11—**The Physician Management Seminar Series: Seminar I.** American College of Physician Executives at the Scottsdale Plaza Resort, Scottsdale. Mon-Fri. Contact: (800) 562-8088.

November 7-11—**The Physician Management Seminar Series: Seminar II.** American College of Physician Executives at the Scottsdale Plaza Resort, Scottsdale. Mon-Fri. Contact: (800) 562-8088.

November 10-12—**7th Annual Techniques in Gynecologic Surgery.** Mayo Clinic-Scottsdale at Marriott's Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

November 14-16—**Hand and Wrist Injuries in the Athlete.** American Society for Surgery of the Hand at Scottsdale. Mon-Wed. Contact: (303) 771-9236.

November 17-19—**Pediatric Orthopaedics: A Comprehensive Course.** American Academy of Orthopaedic Surgeons at The Pointe Hilton Resort at Squaw Peak, Phoenix. Thurs-Sat. Contact: AAOS, (708) 823-7186.

December 2-3—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

December 2-4—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Hyatt Regency, Scottsdale. Fri-Sun. Contact: Karen DeBont, (800) 421-3756.

January 12-13—**2nd Annual Current Topics in Critical Care Medicine.** Mayo Clinic-Scottsdale at the Ritz-Carlton Hotel, Phoenix. Thurs-Fri. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 14-15—**5th Annual Current Topics in Anesthesiology.** Mayo Clinic-Scottsdale at the Ritz-Carlton Hotel, Phoenix. Sat-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 20-22—**Electromyography in Clinical Practice.** Mayo Clinic-Scottsdale. Fri-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 24-26—**1995 Scientific Assemhly—American Academy of Family Practice.** The Pointe Hilton at Tapatio Cliffs, Phoenix. Fri-Sun. Contact: American Academy of Family Practice, Arizona Chapter, (602) 249-2021.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

September 24—**Immunology for the '90s.** Los Angeles Society of Allergy and Immunology at Westin South Coast Plaza Hotel, Costa Mesa. Sat. 8 hrs. Contact: LASAI, PO Box 84443, Los Angeles 90073. (310) 450-6092.

ANESTHESIOLOGY

November 11-13—**Anesthesiology Update: 1994.** UCD at Monterey Plaza, Monterey. Fri-Sun. 14 hrs. $325. Contact: UCD.

November 18-19—**4th Annual Pain Conference.** UCD at Inn at Napa Valley. Fri-Sat. 11 hrs. $300. Contact: UCD.

January 4-7—**Anesthesia Update.** UCSD at Hotel del Coronado, San Diego. Mon-Sat. 21 hrs. $350. Contact: UCSD.

CARDIOLOGY

September 10—**Primary Care Issues in Cardiac and Vascular Disease.** Alta Bates Medical Center at Claremont Resort, Berkeley. Sat. Contact: Caroline Carey, Alta Bates Med Ctr, (510) 204-3884.

September 23-24—**Arrhythmias: Interpretation, Diagnosis, and Management.** American College of Emergency Physicians at Desert Inn, Las Vegas, NV. Fri-Sat. 11 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

October 13-15—**Cardiology Update: 1994.** UCSF at Carmel Valley Resort, Carmel. Thurs-Sat. 18 hrs. Contact: UCSF.

October 27-30—**East Visits West: Coronary Interventions 1994.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sun. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, 403C, La Jolla 92037. (619) 554-8556.

November 18-20—**Arrhythmias: Interpretation, Diagnosis, and Management.** American College of Emergency Physicians at Disneyland Hotel, Anaheim. Fri-Sun. 11 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

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CONTINUING MEDICAL EDUCATION

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DERMATOLOGY

August 28-31—**Advanced Seminars in Dermatology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Wed. Contact: UCD.

November 11-13—**5th Annual Cutaneous Malignancies: 1994 Skin Cancer Update.** Scripps Clinic and Research Foundation at Schaetzel Center for Health Education, La Jolla. Fri-Sun. 16 hrs. Contact: Scripps, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

September 10-11—**ACLS Provider.** CPR Seminars at Antioch. Sat-Sun. CPR Seminars, 1933 Davis St, Ste 297, San Leandro 94577. (510) 632-6135.

September 16—**Advanced Burn Life Support Course.** Torrance Memorial Burn Center at Torrance Memorial Hospital. Fri. 9 hrs. $220. Contact: Nancy Wise, (310) 517-4605.

September 17—**ACLS Recertification.** CPR Seminars at San Francisco. Fri. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro 94577. (510) 632-6135.

September 25-29—**West Coast Emergency Medicine Review Course.** American College of Emergency Physicians and the Emergency Physicians' Medical Group at San Francisco. Sun-Thurs. Contact: EPMG, 1 Montgomery St, Ste 1360, San Francisco 94104. (800) 436-7277.

October 14-16—**Advances in Emergency Medicine.** Continuing Medical Associates at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 17-21—**Emergency Medicine Symposium.** UCSD at San Diego Hilton. Mon-Fri. 17 hrs. $475. Contact: UCSD.

November 7-11—**Emergency Medicine Symposium.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

December 4-9—**15th Annual Conference: Current Concepts in Emergency Care.** American College of Emergency Physicians at Maui Intercontinental Resort, Hawaii. Sun-Fri. 20 hrs. Contact: Kailani World Travel, 4192 Meridian Ave, Box 9751, Bellingham, WA 98227. (800) 544-9269 or (206) 671-1800.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs, (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

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. . . among others

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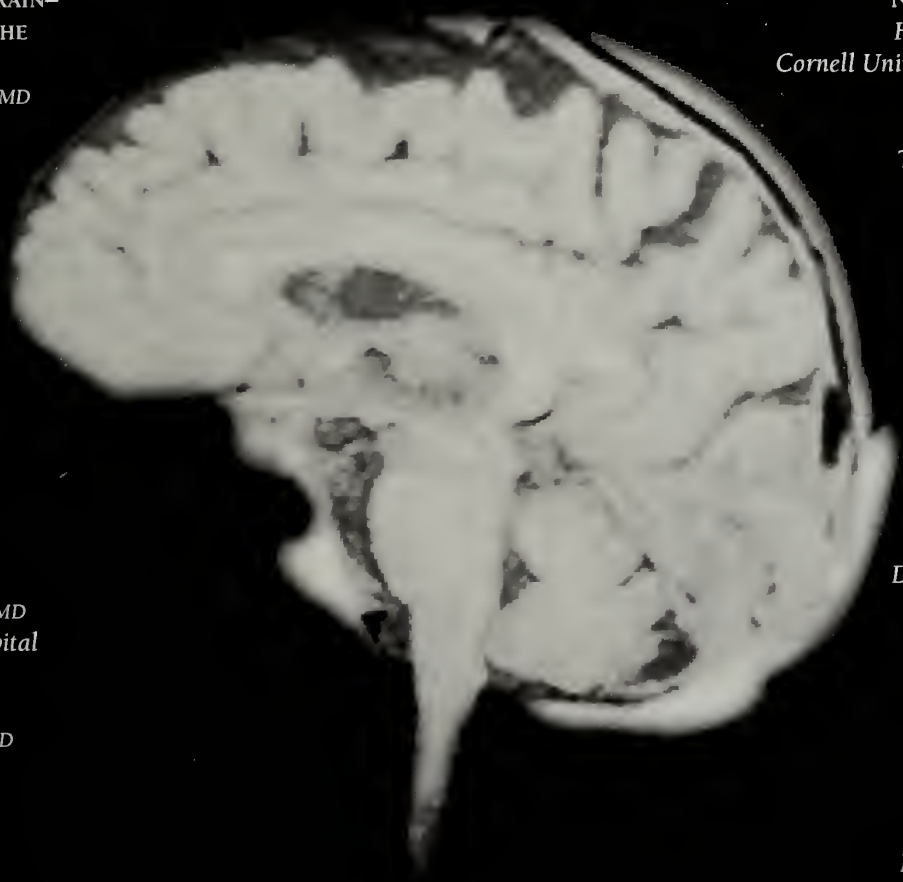

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PROGRAM PROFILE

Center For Musculoskeletal Tumors

Malignant tumors of the musculoskeletal system, whether bone or soft tissue tumors, are extremely rare: only an estimated 4,000 new cases of osteogenic sarcoma, and 6,000 new cases of soft tissue sarcomas of the extremities, are diagnosed each year. Consequently, orthopaedic surgeons in private practice may see a malignant bone tumor perhaps once every 10 years.

In sharp contrast, Lawrence R. Menendez, M.D., associate professor of Orthopaedic Surgery at the University of Southern California School of Medicine and director of Orthopaedic Oncology at USC University Hospital, performs more than 200 procedures a year. This volume, supported by a multidisciplinary team of medical oncologists, musculoskeletal pathologists, vascular and plastic surgeons and radiation therapists, along with nursing, social and rehabilitative services at USC University Hospital, has allowed Dr. Menendez to develop and maintain an expertise in this specialized field.

A CASE STUDY

A 35-year-old law student developed progressive pain in his hip. He eventually fell, sustaining a fracture through his femoral neck. At that time, a big tumor was detected in the proximal third of this femur, with the added complication of spillage into the hip joint. A biopsy confirmed an osteosarcoma, with no evidence of metastatic tumor. After three courses of chemotherapy, the patient underwent surgery.

This was a complicated case because of the tumor spillage. In order to achieve an adequate margin around the tumor, Dr. Menendez not only had to remove the proximal femur and surrounding musculature, but also the entire hip joint en bloc, including acetabulum, as well. Because the patient asked the team to reconstruct a leg that he could walk on and a hip he could move, surgeons opted against a fusion and instead performed a procedure that involved an allograft to reconstruct the acetabulum, and a custom endoprosthesis to replace the joint.

Following surgery, the patient underwent some follow-up chemotherapy. He had essentially 100 percent tumor necrosis, and an excellent response to chemotherapy. His allografts and junctions have since healed, and after a year he is ambulating with a cane — and continuing his pursuit of a law degree.

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University of Southern Californ

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Bone Tumors

Benign and malignant bone tumors each present its own specific treatment challenges, making it imperative that an accurate diagnosis be established. Dr. Menendez treats the most common malignant bone tumor, osteogenic sarcoma, with biopsy and then he develops a comprehensive treatment strategy that may include staging studies, pre- and post-operative treatment with chemotherapy and/or radiation therapy, surgery and reconstruction, rehabilitation, and long-term follow-up to detect tumor recurrence. Reconstruction options include allografts, autologous bone grafts, prosthetic implants or a combination of these materials.

Soft Tissue Tumors

Soft tissue tumors that appear benign may actually be malignant, again requiring absolute accuracy of diagnosis. Oftentimes, large soft tissue resections will require extensive reconstructive surgery involving vascularized flaps to provide tissue coverage. At USC, Dr. Menendez has immediate access to the expertise of vascular surgeons, general surgeons and reconstructive surgeons to provide necessary treatment. As a result, he is prepared for any situation.

Close Contact With Referring Physicians

Follow-up is a vital aspect of the program. Dr. Menendez examines X-rays and exchanges notes with referring physicians, keeping all parties involved. He sends referring physicians a letter every time he sees their patients in follow-up, whether it is a month or five years later. Dr. Menendez follows patients who had malignancies every three months for the first two years, and then every six months. Regular check-ups are recommended for the life of the patient, although Dr. Menendez considers the patient cured if five years pass without a recurrence of metastatic disease.

Lawrence R. Menendez, M.D.:
At the forefront of orthopaedic oncology

About the Director

Lawrence R. Menendez, M.D., predicts that the future of musculoskeletal oncology will be centered within the major academic centers across the country, and believes USC is well-positioned to offer leadership in this complex field.

Born and raised in New Jersey, Dr. Menendez attended Middlebury College in Vermont, where he received his bachelor's degree in biology. He earned his medical degree from the New York University School of Medicine, completed a general surgery internship at Columbia Presbyterian Medical Center, and returned to New York University for his orthopaedic surgery residency. He also did an oncology fellowship at the University of Florida with William F. Enneking, M.D., one of the founders of orthopaedic oncology as a specialty.

From 1985 to 1989, Dr. Menendez served on the full-time USC faculty as assistant professor of Orthopaedic Surgery, and then became a part-time faculty member, moving his private practice to The Hospital of the Good Samaritan in Los Angeles. During this time, he continued to run the orthopaedic oncology service at Los Angeles County+USC Medical Center. In July 1992, he was recruited back to USC full time as associate professor.

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★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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Positron emission tomography (PET) image of ^{11}C-triamcinolone acetonide following intranasal administration of Nasacort[1]

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Provides comfortable, prompt relief of allergic rhinitis and effective QD dosing

- *Nasacort remains in the nasal mucosa with no measurable effect on HPA function* [1-3]*

  Duration of acquisition of the PET image was approximately 55 minutes due to ^{11}C decay ($t_{1/2}$ of 20 minutes).[1] *(n=2)*

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- *Nasacort provides effective QD dosing — 2 puffs/nostril/day effectively controls symptoms in most patients; however, QD dosing can be increased to 4 puffs/nostril/day when necessary*

Please see brief summary of prescribing information on adjacent page.

** In doses up to 440 mcg/day.* [3]

Nasacort...Once Is Enough

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Nasacort® Nasal Inhaler
(triamcinolone acetonide)

For Intranasal Use Only
Shake Well Before Using

BRIEF SUMMARY

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, *e.g.*, joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

The use of Nasacort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Nasacort Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

PRECAUTIONS

General: In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local therapy and discontinuance of treatment with Nasacort Nasal Inhaler.

Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. Nasacort at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see CLINICAL TRIALS section).

Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances.

When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasacort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients being treated with Nasacort Nasal Inhaler should receive the following information and instructions.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Patients should use Nasacort Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations.

Carcinogenesis, Mutagenesis: Animal studies of triamcinolone acetonide to test its carcinogenic potential are underway.

Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m^2/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m^2/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m^2/day or 110 mcg/m^2/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery. Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5 - 15.0 mcg/kg/day or 20 - 110 mcg/m^2/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m^2/day and 7.0 mcg/m^2/day).

Pregnancy: Pregnancy Category C. Like other corticoids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m^2/day in the rat and 320, 640 and 1280 mcg/m^2/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m^2/day). The doses of 0.02, 0.04, 0.08, and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51, and 318.7 times the minimum recommended dose of 110 mcg of Nasacort per day and 3.2, 6.4, 12.7, and 80 times the maximum recommended dose of 440 mcg of Nasacort per day based on a patient body weight of 70 kg. Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Nasacort Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in children below the age of 12. Oral corticoids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS: In controlled and uncontrolled studies, 1257 patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed Nasacort canister. These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days).

The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received Nasacort. Nasal irritation was reported by 2.8% of the patients receiving Nasacort. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received Nasacort and included dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects.

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).

OVERDOSAGE: Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects if the nasal application of the 15 mg of triamcinolone acetonide was administered all at once.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Please see product circular for full prescribing information.

REFERENCES:

1. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc. **2.** Ziemniak JA: Pharmacokinetics of intranasal triamcinolone acetonide. *J Respir Dis* 1991;12 (3, Suppl):S41-S42. **3.** Feiss G, Morris R, Rom D, et al: A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function. *J Allergy Clin Immunol* 1992;89:1151-1156. **4.** Findlay S, Huber F, Garcia J, et al: Efficacy of once-a-day intranasal administration of triamcinolone acetonide in patients with seasonal allergic rhinitis. *Ann Allergy* 1992;68(3):228-232.

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ABSTRACTS AUGUST 1994

(Landrigan PJ, Todd AC: Lead poisoning. West J Med 1994; 161:153-159)

Lead poisoning is the most common disease of environmental origin in the United States today. Adult lead poisoning results primarily from exposure by inhalation in the workplace. Pediatric lead poisoning results principally from the ingestion of lead from environmental media, including paint chips, dust, soil, drinking water, ceramics, and medications. Lead is toxic to many organ systems, among them developing erythrocytes, the kidneys, and the nervous system. Lead-induced toxicity to the central nervous system causes delayed development, diminished intelligence, and altered behavior. In young children, this effect has been demonstrated convincingly to occur at blood lead levels between 10 and 20 mg per dl. The Centers for Disease Control and Prevention has recommended that a blood lead level of 10 mg per dl or higher be considered evidence of increased lead absorption, and the National Academy of Sciences has concurred in that recommendation. Unresolved issues in need of further study include the frequency of screening young children for lead, the question of whether women should be offered screening for lead before conceiving a pregnancy, the role of x-ray fluorescence analysis in assessing lead in bone, and the appropriate legislative response of the United States government to lead-based paint abatement.

LEAD POISONING

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LEAD POISONING

Three copies of this abstract are provided to help you in filing and cross-referencing research articles.

CONTINUING MEDICAL EDUCATION

(Continued from Page 121)

December 12-16—**Emergency Medicine Symposium.** UCSD at Basic Science Building. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 16-20—**Emergency Medicine Symposium.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 24-29—**California Trauma Conference.** UCSD at Hyatt Regency, San Diego. Tues-Sun. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

November 5—**Neurology for Primary Care.** UCD at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. $95. Contact: UCD.

December 9-11—**Neurology for the Non-Neurologist.** American College of Emergency Physicians at Desert Inn, Las Vegas, Nevada. Fri-Sun. 12 hrs. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

December 24-29—**Advances in Medicine '94.** American Academy of Family Physicians and Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Lahaina, Maui, Hawaii. Sat-Thurs. 16 hrs. Contact: Joe Harrison, MD, PO Box 10185, Lahaina, HI 96761. (808) 878-6757.

January 20-22—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

1994—**HIV Primary Care Mini-Residency.** UCSD at Owen Clinic, San Diego. Ongoing. 30 hrs. Contact: UCSD.

GERIATRICS

October 7-8—**Coming of Age: Geriatrics for the Primary Care Provider—Part II.** UCD at Sacramento Inn. Fri-Sat. 13 hrs. $235. Contact: UCD.

November 7-9—**Geriatrics Update: 1994.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Mon-Wed. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

1994—**Mini-residency in Geriatrics.** UCSD at Multi Purpose Facility, San Diego. Ongoing. 40-80 hrs. $195. Contact: UCSD.

1994—**The GGG/Alzheimer's Family Center: Sharing the Caring—Training Series on Dementia.** UCSD. Ongoing. 4 hrs. $25. Contact: UCSD.

INFECTIOUS DISEASE

November 4-6—**Advances in Infectious Disease.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

August 26-September 1—**Comprehensive Nephrology Review Course.** UCLA School of Medicine at Beverly Hilton Hotel, Beverly Hills. Fri-Thurs. 51 hrs. $895. Contact: UCLA.

September 17-19—**1994 International Symposium on Bone Marrow Transplantation.** Sutter Community Hospital at Fairmont Hotel, San Francisco. Sat-Mon. Contact: Sutter Community, 2800 L St, Sacramento 95816. (800) 777-0231.

October 1—**Focus on Venous Access: Hemodialysis, Pheresos, Chemoinfusion.** UCSD at Le Meridien Hotel, Newport Beach. Sat. 8 hrs. $125. Contact: UCSD.

October 22—**Diabetes.** Sutter Community Hospitals at Sacramento. Sat. Contact: Peggy Coit, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

OB/GYN

October 1—**Colscopy.** Sutter Community Hospitals at Sacramento. Sat. Contacat: Lynne MacRae, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

October 1-2—**6th Annual Ultrasound Update: 1994.** UCD at Red Lion Inn, Sacramento. Sat-Sun. 10 hrs. $240. Contact: UCD.

October 8—**Women's Health.** Sutter Community Hospitals at Stockton. Sat. Contact: Catherine Davis, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

December 1-3—**Obstetrics and Gynecology Conference.** University of Nebraska Medical Center at Bally's, Las Vegas, Nevada. Thurs-Sat. $275. Contact: UNMC, 600 S 42nd St, Omaha, NE 68198-5651. (800) 642-1095 or (402) 559-4152.

OCCUPATIONAL/ENVIRONMENTAL

September 22-25—**Emerging Issues in Occupational and Environmental Health.** American College of Occupational and Environmental Medicine and the Western Occupational and Environmental Medical Association at Stouffer Stanford Court Hotel, San Francisco. Thurs-Sun. Contact: WOEMA, 50 First St, Ste 300, San Francisco 94105. (415) 764-4803.

ONCOLOGY

September 25-27—**State of Breast Cancer 1994: An Interactive Symposium.** UCSF at Sheraton Palace Hotel, San Francisco. Sun-Tues. 20 hrs. $350. Contact: UCSF.

October 6-8—**18th Annual Physicians Cancer Symposium.** Scripps Memorial Hospital at Stevens Cancer Center, San Diego. Thurs-Sat. 16.5 hrs. $390. Contact: Cancer Symposium, 2603 Main St, Ste 690, Irvine 92714. (800) 321-6338.

OPHTHALMOLOGY

September 23-25—**13th Annual Educational Conference.** California Association of Ophthalmology at Ritz-Carlton, Huntington Hotel, Pasadena. Fri-Sun. 11 hrs. Contact: CAO, 605 Market, Ste 1109, San Francisco 94105-3213. (415) 777-3937.

OTOLARYNGOLOGY

September 11-16–October 9-14—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 53 hrs. $875-$1,100. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

November 3-5—**Otolaryngology Update: 1994.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17 hrs. $425. Contact: UCSF.

PATHOLOGY

September 17—**34th Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at La Jolla Marriott. Sat. Contact: National Kidney Foundation, 5777 W. Century Blvd, Ste 395, Los Angeles 90045-7404. (310) 641-8152.

September 17-21—**9th Combined Skin Pathology Course and 5th Annual Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Sat-Wed. 40 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

September 21-24—**Surgical Pathology of the Lung.** American Society of Clinical Pathologists at Sheraton Hotel Fisherman's Wharf, San Francisco. Wed-Sat. Contact: ASCP, 2100 W Harrison St, Chicago, IL 60612-3798. (800) 621-4142.

November 13-16—**Clinical Microbiology Update.** American Society of Clinical Pathologists at Pan Pacific Hotel, San Diego. Sun-Wed. Contact: ASCP, 2100 W Harrison St, Chicago, Il 60612-3798. (800) 621-4142.

PEDIATRICS

October 1—**Therapy for Childhood Neuromuscular Diseases.** Children's Hospital and Health Center at Hyatt Regency, San Diego. Sat. 6.5 hrs. $75. Contact: CAM, 3030 Children's Way, San Diego 92123. (619) 576-5819.

October 22—**Pediatrics.** Sutter Community Hospitals at Auburn. Sat. Contact: Lynne MacRae, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

October 29—**Ambulatory Pediatrics.** UCD at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. $95. Contact: UCD.

October 29—**Pediatric Otology Update 1994.** Children's Hospital Oakland. Sat. Contact: Hearing Institute Foundation, 2120 Forest Ave, #2, San Jose 95128. (408) 288-7777.

December 1-4—**Society of ENT Advances in Children.** UCD at Radisson Hotel, Sacramento. Thurs-Sun. 10 hrs. Contact: UCD.

December 3—**13th Annual Binational Pediatric Conference.** Children's Hospital San Diego and American Academy of Pediatrics at Mercy Hospital Educational Center, San Diego. Sat. $45. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

January 21-28—**Pediatric Emergencies.** UCSD at Kona, Hawaii. 21 hrs. $460. Contact: UCSD.

(Continued on Page 132)

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(Continued from Page 130)

January 23-27—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital San Diego at Town and Country Hotel, San Diego. Mon-Fri. $395. Contact: Children's Hospital, MC 5016, 3020 Children's Way, San Diego 92123. (619) 495-4940.

PHYSICAL MEDICINE/REHABILITATION

October 8-12—**56th Annual Assembly, American Academy of Physical Medicine and Rehabilitation** at Anaheim Hilton Hotel and Towers and Anaheim Convention Center. Sun-Wed. Contact: AAPMR, 122 S Michigan Ave, Ste 1300, Chicago, IL 60603-6107. (312) 922-9366.

PSYCHIATRY

September 30-October 4—**Power of the Art: Introduction to Medical Hypnosis and Other Practical Wisdoms.** UCSD at Sheridan Grande, San Diego. Fri-Tues. 26 hrs. $550. Contact: UCSD.

October 7-11—**The Power of the Art: Introduction to Medical Hypnosis and Other Practical Wisdoms.** UCSD at Colonial Inn, La Jolla. Fri-Tues. 26 hrs. Contact: UCSD.

October 14-15—**Psychopharmacology Clinical Research Update.** UCD at Hilton Hotel, San Francisco. Fri-Sat. 14 hrs. $395. Contact: UCD.

1994—**Basic Clinical Hypnosis Training.** UCSD at La Jolla. Ongoing. 30 hrs. $245. Contact: UCSD.

PULMONARY MEDICINE

September 23-25—**Diagnosis and Management of Respiratory Diseases.** American College of Emergency Physicians at Esmeralda Resort, Palm Springs. Fri-Sun. 12 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

October 13-15—**Pulmonary and Critical Care Medicine.** UCSF at Ana Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

RADIOLOGY

August 25-28—**Physics of Diagnostic Radiology.** UCD on Campus. Thurs-Sun. Contact: UCD.

September 8-10—**Trauma and Emergency Radiology.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 16 hrs. $395. Contact: UCSF.

September 29–October 1—**Interventional Hepatobiliary Radiology.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 18 hrs. $550. Contact: UCSF.

October 2—**Oncologic Imaging Update.** UCSF at Fairmont Hotel, San Francisco. Sun. 6.5 hrs. $150. Contact: UCSF.

October 3-7—**Clinical Magnetic Resonance Imaging.** UCSF at Fairmont Hotel, San Francisco. Mon-Fri. 33 hrs. $595. Contact: UCSF.

October 7-8—**Vascular Ultrasound: State of the Art.** UCSF at Fairmont Hotel, San Francisco. Fri-Sat. 13.5 hrs. $295. Contact: UCSF.

October 10-14—**Neuroimaging Visiting Fellowship Program.** Stanford School of Medicine. Mon-Fri. 40 hrs. Contact: Barbara Platt, (415) 723-4733.

October 15-16—**Neuroradiology Update.** UCSD at Hotel del Coronado. Sat-Sun. Contact: UCSD.

October 17-19—**Radiology for the Non-Radiologist.** UCSD at Hyatt Regency, La Jolla. Mon-Wed. 20 hrs. $450. Contact: UCSD.

October 17-21—**19th Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. Contact: UCSD.

October 21-23—**14th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. Contact: UCSD.

October 31–November 4—**Diagnostic Radiology Seminars.** UCSF at Ritz-Carlton Kapalua, Maui, Hawaii. Mon-Fri. 26 hrs. $595. Contact: UCSF.

November 14-18—**A Practical Approach to Breast Imaging.** UCSF at Ritz-Carlton, Rancho Mirage. Mon-Fri. 20 hrs. $595. Contact: UCSF.

December 8-10—**Magnetic Resonance Angiography in Clinical Practice with CTA Correlation.** UCSF at Ritz-Carlton, Rancho Mirage. Thurs-Sat. 12.5 hrs. $425. Contact: UCSF.

December 11-16—**A Practical Approach to Breast Imaging.** UCSF at Ritz-Carlton Kapalua, Maui, Hawaii. Sun-Fri. 20 hrs. $595. Contact: UCSF.

1994—**Fellowship in Interventional Radiology for Radiologists.** UCSD Medical Center. Ongoing. 40 hrs. $700. Contact: UCSD.

1994—**Visiting Fellowship in Magnetic Resonance Imaging.** UCSD at MR Institute, San Diego. Ongoing. 40 hrs. $1,200. Contact: UCSD.

1994—**Visiting Fellowship for Physicians and Sonographers in Duplex Ultrasound: Focus on Carotid and Deep Venous Thrombosis.** Ongoing. 30 hrs. $600. Contact: UCSD.

1994—**Visiting Fellowship Program of Endovaginal Sonography: Focus on Techniques and Application.** UCSD Medical Center. Monthly. 30 hrs. $600. Contact: UCSD.

SLEEP MEDICINE

January 28—**Sleep Medicine: Practices for the 21st Century.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

SURGERY

September 9-13—**Summer Institute—Intensive Surgical Skills.** American Academy of Orthopedic Surgeons at Monterey Conference Center, Marriott Hotel and Doubletree Hotel, Monterey. Fri-Tues. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

October 29—**Suture Workshop.** Sutter Community Hospitals at Sacramento. Sat. Contact: Catherine Davis, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

GENERAL/MULTIDISCIPLINARY

October 27-30—**1994 CME/Golf Meeting.** Nevada Academy of Family Physicians at Sheraton Desert Inn Hotel & Casino, Las Vegas. Thurs-Sun. 21 hrs. Contact: Barbara Bolling, NAFP, PO Box 27713, Las Vegas, NV 89126-1713. (702) 647-0117.

January 19-22—**Medicine Meets Virtual Reality II: Interactive Technology & Healthcare.** UCSD. Thurs-Sat. Contact: UCSD.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

September 16-18—**Sixth National Conference on Outreach Education: The Changing Colors of Outreach Education.** University of Colorado Health Sciences Center at Tamarron Resort, Durango. Fri-Sun. Contact: U of Colo.

September 16-18—**Third Annual Medical Ethics Conference.** University of Colorado Health Sciences Center at Aspen. Fri-Sun. Contact: U of Colo.

September 23-24—**23rd Annual Montrose Fall Clinics.** Montrose Memorial Hospital, Pavilion at Montrose. Fri-Sat. Contact: Kathy Holman, (303) 240-7397.

September 23-24—**Penrose Cancer Conference.** Penrose-St Francis Health-Care System at Broadmoor Hotel, Colorado Springs. Fri-Sat. Contact: Leslie Bent, (719) 577-2510 or (719) 630-5271.

September 30—**Rocky Mountain Regional Cardiovascular Disease Conference.** University of Colorado Health Sciences Center at Vail. Fri. Contact: U of Colo.

October 24-28—**Prevention in Practice: Workplace Health in the 21st Century.** American College of Occupational and Environmental Medicine at Denver Marriott City Center, Denver. Mon-Fri. Contact: ACOEM, (708) 228-6850.

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January 28-February 2—**24th Annual Mid-Winter Conference of Colorado Ophthalmological Society.** Sheraton Steamboat, Steamboat Springs. Sun-Thurs. Contact: David R. Scott, (800) 394-4968.

February 20-24—**19th Midwinter Symposium on Practice Surgical Challenges in Otolaryngology.** University of Illinois College of Medicine at Snowmass. Mon-Fri. Contact: Jane Whitener, (312) 996-5751.

February 26-March 3—**Ninth Annual Cardiology for the Clinician Conference: Practical Guidelines for Merging Advances in Cardiology and Bedside Medicine.** University of Illinois College of Medicine at Snowmass. Mon-Fri. Contact: Sue Talbert, (312) 996-4631.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 270-6761.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 16-17—**Annual Meeting—American College of Surgeons, New Mexico Chapter.** Hotel de Santa Fe, Santa Fe. Contact: Bonnie Smith, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237.

September 17—**Management of Patient with Cardiac Disease.** Journal Center, Albuquerque. Sat. Contact: Tracy L. Green, New Mexico Heart Clinic, (505) 841-1000.

October 5-9—**3rd Annual New Mexico Medical Computer Course.** Holiday Inn Pyramid Hotel, Albuquerque. Contact: Floyd Smith, NMOMA, PO Box 90396, Albuquerque 87199-0396. (505) 828-1905.

October 8-9—**What Is New With the Newborn?** New Mexico Pediatric Society at Snakedance, Taos Ski Valley. Contact: Richard Rolston, MD, (505) 898-7898.

October 28-29—**ECG Interpretation for the Primary Care Physician.** Journal Center, Albuquerque. Fri-Sun. Contact: Tracy L. Green, New Mexico Heart Clinic, (505) 841-1000.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

September 21-24—**Utah Medical Association—Annual Meeting.** University Park Hotel, Salt Lake City. Wed-Sat. Contact: Utah Medical Association.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 133)

September 9—**Interventional Radiology.** Seattle. Fri. Contact: U/W.

September 9-11—**Radiation Health Effects and Hanford: A Joint Conference for Concerned Citizens and Health Care Providers.** Spokane. Fri-Sun. Contact: U/W.

September 10-11—**Pediatric Advanced Life Support.** Seattle. Sat-Sun. Contact: Children's, (206) 368-4802.

September 11-16—**North Pacific Pediatric Society—149th Meeting.** Blaine. Sun-Fri. Contact: Norma Brooks, (206) 248-2229.

September 19-23—**Annual Advances in Family Practice.** Seattle. Mon-Fri. Contact: U/W.

September 19-23—**Annual Advances in Family Practice.** Seattle. Mon-Fri. Contact: U/W.

September 21—**Pneumonia Symposium.** Seattle. Wed. Contact: Providence, (206) 320-2552.

September 29-30—**Update: Common Urinary Tract Problems in Children.** Seattle. Thurs-Fri. Contact: Children's, (206) 526-2501.

October 6—**Sleep Symposium.** Seattle. Thurs. Contact: Providence, (206) 320-2552.

October 14—**Radiation Oncology Symposium.** Seattle. Fri. Contact: Providence, (206) 320-2552.

October 15—**Arthrocentesis & Injection Techniques.** Seattle. Sat. Contact: U/W.

October 15—**Interventional Radiology.** Seattle. Sat. Contact: U/W.

October 20—**Cancer Care Symposium.** Seattle. Thurs. Contact: Providence, (206) 320-2552.

October 21-22—**Transplant Opportunities.** Seattle. Fri-Sat. Contact: Providence, (206) 320-2552.

October 27—**Cancer Care Symposium.** Seattle. Thurs. Contact: Providence, (206) 320-2552.

October 27-30—**7th Annual Pediatric Critical Care Colloquium.** Seattle. Thurs-Sun. Contact: Children's, (206) 526-2501.

October 28-29—**Mental Health Update.** Seattle. Fri-Sat. Contact: U/W.

November 3-4—**Current Concepts in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 4—**Muscular Dystrophy and Related Disorders.** Seattle. Fri. Contact: Children's, (206) 526-2501.

November 10—**Family Practice Symposium.** Seattle. Thurs. Contact: Providence, (206) 320-2552.

November 11-12—**Pediatric Advanced Life Support.** Seattle. Fri-Sat. Contact: Children's, (206) 368-4802.

December 2—**Pediatric Update.** Seattle. Fri. Contact: Children's, (206) 526-2501.

December 7-10—**American College of Physicians.** Seattle. Wed-Sat. Contact: U/W.

December 8-10—**10th Annual Infectious Disease Conference.** Seattle. Thurs-Sat. Contact: Pacific Northwest Medical Education Institute, (206) 261-2160.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762. ◆

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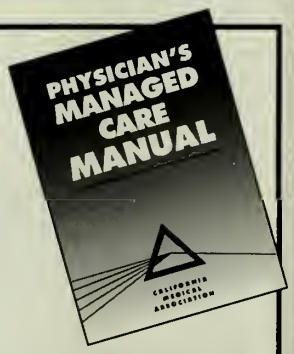

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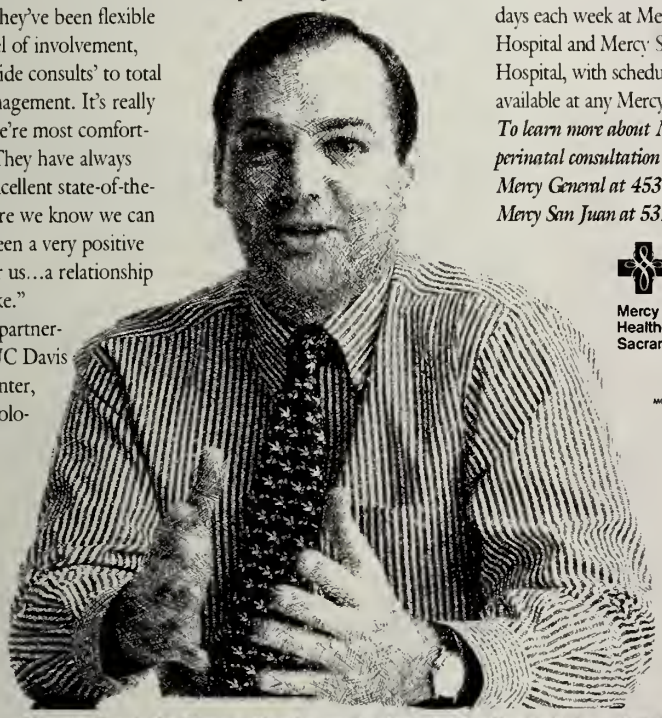
To learn more about Mercy's perinatal consultation services call Mercy General at 453-4140 or Mercy San Juan at 537-5339.



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Lower Respiratory Tract Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Otitis Media* caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Sinusitis* caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Skin and Skin Structure Infections* caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp. *Urinary Tract Infections* caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp. While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies to determine the causative organisms and their susceptibility to *Augmentin* should be performed together with any indicated surgical procedures. Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once results are known, adjust therapy, if appropriate.

Contraindications: Patients with a history of allergic reactions to any penicillin, or patients with a history of *Augmentin*-associated cholestatic jaundice/hepatic dysfunction.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH *AUGMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.** Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis." After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. Use *Augmentin* cautiously in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with *Augmentin* use is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications (see CONTRAINDICATIONS and ADVERSE REACTIONS—*Liver*).

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were mild and transient; <3% of patients discontinued therapy because of them. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis, mucocutaneous candidiasis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis). These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (see WARNINGS). A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. Interstitial nephritis and hematuria have been reported rarely. Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*. Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

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† Latest available annual data: January to December 1991.

‡ *In vitro* susceptibility does not necessarily imply *in vivo* efficacy.

Please see brief summary of prescribing information for contraindications, warnings, precautions and adverse reactions on adjacent page.

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Articles

Firearms in New Mexico

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To determine the prevalence of firearm ownership and storage practices in New Mexico, we did a random-digit-dialing survey of New Mexico residents in October 1991. Of 200 households surveyed, 79 (40%) had 1 or more firearms in the home. Rural households were more likely than urban households to have firearms (44% versus 30%), and households with annual incomes of greater than $25,000 were more likely to have a firearm than households with incomes of $25,000 or less (41% versus 33%). Household firearm ownership did not vary with the presence of young (<15 years old) children (38% with children versus 41% without). Handguns were generally owned for self-protection, and rifles were owned for hunting. Of households with firearms, 24% stored them unsafely (unlocked and loaded or unloaded but with ammunition nearby), including 21% of households with young children. Of the households with handguns only, 40% stored these firearms unsafely compared with 13% of those with rifles only. The prevalence of gun ownership in New Mexico is similar to that reported in national surveys; handguns are stored less safely than rifles; and the presence of young children in the home does not appear to improve firearm storage safety.

(Wiktor SZ, Gallaher MM, Baron RC, Watson ME, Sewell CM: Firearms in New Mexico. West J Med 1994; 161:137-139)

Deaths due to firearms are a major public health problem in New Mexico. In the five-year period from 1985 to 1989, 1,488 New Mexicans died of firearm-related causes, and these deaths represent the sixth leading cause of death in New Mexico.[1] Easy availability of firearms is considered to be a risk factor for suicides as well as for homicides.[2,3] New Mexico's suicide rate is twice the rate of the nation, and in 1991, two thirds (66%) of suicides were completed by firearms (Annual Report, New Mexico Office of the Medical Investigator, 1991). New Mexico's adjusted homicide rate is the highest in the United States,[4] and in 1991, 51% of homicides were carried out by firearms (Annual Report, NM Office of the Medical Investigator, 1991). Unsafe storage of firearms in locations easily accessible to young children increases the likelihood of unintentional injury and death in this group.[5] Firearms are the fourth leading cause of death from unintentional injury among young children in New Mexico. More than 90% of these deaths occur among children who are playing with loaded firearms in the home.[6]

Despite the severity of this problem, little is known about the prevalence of firearm ownership and storage practices in New Mexico. This survey was carried out to assess the prevalence of firearm ownership in New Mexico and to characterize firearm storage practices.

Methods

In October 1991, a random-digit-dialing telephone survey of New Mexico residents was carried out by staff of the University of New Mexico Tumor Registry using methods developed for the Behavioral Risk Factor Surveillance System.[7] All New Mexico residents aged 18 years and older and owning a telephone were eligible. Respondents were asked whether any firearms were kept in the house and, if so, the number of firearms, the type, and the storage location of each firearm and whether each was locked. No attempt was made to identify the firearm purchaser or owner.

Additional information was collected on demographic characteristics of the respondent and the household. The ethnicity of the respondent was used as a surrogate for household ethnicity. County of residence was classified as urban or rural based on the 1990 census. Children younger than 15 years were defined as young children. Because the demographic information collected in the survey applied to the respondent, and this person was not necessarily the firearm owner, only household variables could be used to characterize firearm owners.

Households were classified into four storage-safety groups based on the least safely stored firearm in the household. In decreasing order of safety, these categories are as follows:

- All firearms stored locked,
- At least one firearm stored unloaded and unlocked with no ammunition nearby and no other firearm stored in a less safe manner,

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- At least one firearm stored unloaded and unlocked with ammunition stored nearby, and
- At least one loaded firearm stored unlocked.

For example, a household with three guns in which one was stored locked, one stored unlocked and unloaded, and one loaded and unlocked would be classified into the fourth group. For the purpose of this analysis, the first two categories are considered safe storage, whereas the last two categories of storage are considered unsafe. Data analysis was performed using Epi Info software.[8] Prevalence ratios,[9(p147)] 95% confidence intervals, and two-tailed Fisher's exact test were used as measures of association.

Results

Of 274 households with an eligible respondent, 200 (73%) were surveyed, and 74 (27%) refused to participate. An additional 12 households had no eligible respondents. Of the survey respondents, 56% were non-Hispanic whites, 35% were Hispanic whites, and the remaining 9% included Native Americans, blacks, and Asians. This racial or ethnic distribution is similar to that reported in the 1990 census for New Mexico except for an underrepresentation of Native Americans: 4% of the survey respondents compared with 9% in the census. Two thirds of respondents (66%) were female compared with 50% of the New Mexico population based on the 1990 census.

Of the 200 households, 79 (40%; 95% confidence interval, 33% to 46%) had at least one firearm in the house. Of non-Hispanic white households, 44% had guns compared with 33% of Hispanic households and 39% of the households made up by other ethnic groups (Table 1). Of the rural households, 44% reported owning firearms compared with 30% of urban households. Households with annual incomes of more than $25,000 had a higher prevalence of gun ownership (56%) than did households with lower incomes (30%). Firearm ownership did not vary by whether a young child lived in the house (38%) or not (41%).

TABLE 1.—*Prevalence of Firearm Ownership by Household Characteristics, New Mexico, 1990*

Characteristic	Total Households, No.	Households With Firearms No.	%	Prevalence Ratio	95% Confidence Interval
Racial or ethnic group					
Non-Hispanic white	112	49	44	1.3	0.9, 2.0
Other	18	7	39	1.2	0.6, 2.3
Hispanic white	70	23	33	1	Referent
Residence					
Rural	133	59	44	1.5	1.0, 2.2
Urban	67	20	30	1	Referent
Household income*					
>$25,000	73	41	56	1.9	1.3, 2.7
≤$25,000	112	33	30	1	Referent
Child <15 years old in house					
Yes	85	32	38	0.9	0.6, 1.3
No	115	47	41	1	Referent

*Some respondents declined to answer the question.

TABLE 2.—*Prevalence of Unsafe Firearm Storage by Selected Factors, New Mexico, 1990*

Factor	Households With Firearms, No.	Households With Unsafe Storage No.	%	Prevalence Ratio	95% Confidence Interval
Child <15 years old in house					
Yes	23	6	21	0.7	0.3, 1.4
No	41	13	32	1	Referent
Type of firearm owned*					
Handgun only	15	6	40	3.1	0.9, 10.4
Handgun and rifle	32	10	31	2.4	0.7, 7.8
Rifle only	23	3	13	1	Referent

*Nine respondents declined to answer the question.

Of the 79 households with firearms, 18 (23%) had only handguns in the house; all except 1 of these 18 households had only one handgun. In all, 25 households (32%) had only rifles, 32 (40%) had both handguns and rifles, and 4 households (5%) did not identify the type of firearm(s) owned.

The principal reason for owning firearms varied by type of firearm. Self-protection was the reason for 11 of the 18 households (61%) with handguns only, compared with 1 of the 25 households (4%) with rifles only. Of the 36 households with both types of firearms, 11 (31%) reported their use for self-protection. Hunting was the principal reason for gun ownership in 80% of households with rifles only, 58% of households with both types of firearms, and 6% of households with handguns only. Other reasons given for owning firearms were target practice, gun collecting, and protection of farm animals.

Figure 1 shows the distribution of firearm storage practices. Of the 79 households with firearms, 51 (65%) reported storing their firearms safely, 19 (24%) reported unsafe firearm storage, and 9 (11%) household respondents were either unwilling or unable to indicate storage practices.

Households with young children had a lower prevalence of unsafe storage (21%) compared with households with no young children (32%), although this difference was not statistically significant ($P = .42$) (Table 2). Of households with handguns only, 44% reported storing their firearms unsafely compared with 13% of households with rifles only and 31% of households with both types of firearms.

A total of 12 loaded-unlocked firearms were stored in 10 different households; 1 household had loaded-unlocked guns stored in three separate locations. Storage locations included closets, drawers, gun cabinets, and under beds.

Discussion

In our survey, 40% of households owned guns, compared with an estimated 50% prevalence nationwide and 38% in Texas.[10,11] Easy access to firearms in the home in-

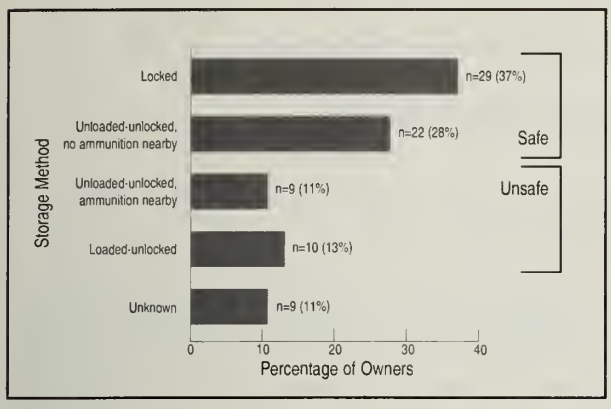

Figure 1.—The graph shows the distribution of firearm storage methods in 79 firearm-owning New Mexico households. Households were classified by the least safely stored firearm.

creases the likelihood of homicides, suicides, and unintentional injury deaths.[2,3,5] Given the high prevalence of gun ownership among New Mexico households, a significant number of people are at risk for firearm injury or death. The major strategy to deal with existing firearms is education. Educational efforts need to be broadly targeted. School-based education could target children who may have access to and play with guns in the home. Physicians can elicit information on guns in the home when seeing patients for well-child care or any other reason. Educational strategies could also provide information on gun storage and safety practices targeted at current and new gun owners. Other strategies to deal with the threat from firearms have been proposed, including legislation to limit gun ownership and design changes to prevent the unintentional firing of a gun.[12] Survey results such as these can help direct educational efforts toward groups with a higher prevalence of gun ownership and evaluate efforts to reach such groups.

Studies of unintentional firearm deaths in children indicate that most of these deaths occur in homes with improperly stored firearms.[5] In New Mexico, more than 90% of unintentional firearm deaths in children younger than 12 years occurred when a child found a loaded, unlocked firearm in the home.[6] In our survey, 38% of households with young children had a firearm in the home, and in 21% of these households, the firearm was stored unsafely. Review of the storage locations of loaded-unlocked guns identified sites that are easily accessible to children. Educational efforts should promote safer firearm storage practices. Furthermore, physicians should discuss firearm safety during routine well-child visits, a practice that is currently rarely carried out.[11]

The improper storage of firearms in the home also increases the risk of suicides[13]; however, its role in homicide risk is less clear. These deaths are often the result of impulsive behavior in response to a family argument or temporary crisis. The frequent spontaneity of events leading to these deaths suggests that ready access to a loaded firearm may be an important risk factor.

Previous studies indicate that handguns are more often stored unsafely than rifles and are more often involved in intentional and unintentional firearm deaths.[5,14] In our survey, households with handguns only were three times more likely to report unsafe firearm storage than households with rifles only. This may be partly explained by the fact that most handguns are purchased for self-protection and therefore kept readily accessible.

One limitation of the study design is that only homes with telephones were represented in this survey. According to the 1990 census, 16% of homes in New Mexico do not have telephones, which is higher than the national rate. Such households may differ substantially from those with telephones with respect to firearm ownership and storage. A second limitation is the high refusal rate (27%) because households that refused to participate may also differ substantially from those that participated. The reasons for this high refusal rate are unclear because other surveys have found much lower refusal rates for questions regarding firearm ownership.[15] A third limitation is that we could not validate the responses concerning firearm ownership and storage. Others, however, have found excellent agreement between firearm-ownership surveys and firearm registration records.[16] A fourth limitation is the small sample size, which limited the description and analysis by racial or ethnic subgroups. Finally, we were not able to gather specific information regarding the owner of the firearms, preventing us from fully describing demographic differences between owners and nonowners.

Despite these limitations, this survey is a valuable first step in defining the prevalence of gun ownership and storage practices in New Mexico, and we hope it will stimulate efforts to address the hazards of gun ownership in the home and to assess the effects of interventions that promote safe gun storage.

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Articles

Helping Pregnant Teenagers

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Teenagers who are pregnant face many difficult issues, and counseling by physicians can be an important source of help. We suggest guidelines for this counseling, beginning with a review of the scope and consequences of adolescent pregnancy. Communication strategies should be aimed at building rapport with techniques such as maintaining confidentiality, avoiding judgmental stances, and gearing communication to cognitive maturity. Techniques for exploring family relationships are useful because these relationships are key influences on subsequent decisions and behaviors. We discuss topics related to abortion and childbearing, such as safety, facilitation of balanced decision making, the use of prenatal care, and the formulation of long-term plans. Physicians who can effectively discuss these topics can help pregnant teenagers make informed decisions and improve their prospects for the future.

(Bluestein D, Starling ME: Helping pregnant teenagers. West J Med 1994; 161:140-143)

Adolescent pregnancy is an endemic social concern with damaging health consequences. This harmful potential generates costs exceeding $20 billion a year.[1] Physicians can intervene as advocates of prevention of teenage pregnancy. The importance of another key intervention, counseling the already-pregnant teenager, is less widely appreciated. Delivered effectively, such counsel can promote satisfaction with abortion decisions, early prenatal care when a pregnancy is continued, and positive goal setting after the child is born.

Unlike other recent reviews, which primarily address preventing teenage pregnancy, we discuss counseling adolescents once pregnancy has occurred.[2-6] Our specific objectives are to provide requisite background, offer guidelines for building rapport, and identify issues pertinent to subsequent decision making.

The Scope of the Problem

Pregnancy, abortion, childbearing, and single parenthood rates in the United States are the highest among industrialized countries.[7] Key reasons include ambivalence about contraception as well as media influences that support adolescent sexuality. Substance abuse, physical and sexual abuse, family dysfunction, anxiety, and depression also predispose an adolescent to pregnancy and determine its consequences.[3,8] For some teenagers, pregnancy and childbearing are experimentation and risk-taking behaviors, abetted by attaining reproductive capacity in advance of cognitive and emotional maturity.[4] Teens who grow up in poverty or experience discrimination as members of minority groups may not perceive viable opportunities for educational or occupational advancement. They may be unwilling to defer childbearing because they see motherhood as the only adult role open to them.[5] In sum, adolescent pregnancy reflects underlying and ongoing tensions in American society. As these tensions will persist for the foreseeable future, the need to counsel already-pregnant teenagers will remain.

The need for such counseling is also evident from adolescent pregnancy rates.[9-12] With more than a million teen pregnancies annually, 1 in 10 American teenagers will conceive each year. Of these pregnancies 85% are unplanned, resulting in 400,000 abortions a year. Another 100,000 miscarry, and 500,000 pregnancies are continued to term. Much of this childbearing occurs outside marriage and is associated with ongoing poverty. Childbearing rates are highest for African-American, inner-city teenagers, but are rising rapidly among other racial and ethnic groups.[10,13] These births are increasingly to younger teenagers (ages 14 to 16), the group most likely to suffer medical and social adversity.[4] These include second-trimester abortions, which are more costly and traumatic than first-trimester terminations, or carrying an unwanted pregnancy to term.[14] Childbearing teenagers face a 60% excess in maternal mortality compared to adults and are more likely to suffer toxemia, anemia, hemorrhage, cervical trauma, cephalopelvic disproportion, excessive weight gain, and premature labor.[11] These complications are not inherent in the biologic aspects of adolescence, however. They are due more to social and behavioral correlates of adolescence, such as inadequate prenatal care, poor nutrition, substance abuse, or emotional distress, than to physiologic immaturity unless a teen is younger than age 15.[3] Infants born to teenage mothers are at substantially increased risk for prematurity or low birth weight and, consequently, for mortality and neurodevelopmental mor-

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bidities.[10] A maternal age of 16 or less doubles the likelihood of low birth weight and triples infant mortality in the first month of life.[6] The mortality for infants born to young African-American women in this age group is nearly double the national average of 7.6 per 1,000 live births.

Unrecognized obstetrical injuries can predispose these children to subsequent academic or behavioral difficulties, along with inadequate parenting, unstable social environments, and socioeconomic disadvantage, in some instances.[15] Childbearing in adolescence can also prevent or delay educational and occupational advancement for many women.[8]

Communication Strategies

Many of the results of adolescent pregnancy can be improved with early pregnancy diagnosis and timely abortion or prenatal care. Pregnant adolescents delay health care, however, in part because services may be unavailable, inaccessible, unaffordable, or not geared to their needs.[16] Delay can also result from teenagers' unfamiliarity with pregnancy symptoms, not realizing the importance of early care, and emotional reactions such as denial, embarrassment, guilt, and fear.[17,18]

Teenagers are more likely to seek prompt follow-up and accept other health-promoting suggestions if they trust the source of this advice.[19] Building trust requires effective communication, the first prerequisite of which is guaranteed confidentiality.[20] Specifically, a teenager needs to know that her physician will not disclose the pregnancy without permission. This stance is congruent with the policies of the American Medical Association, of specialty organizations such as the American Academy of Family Physicians, and the "emancipated" legal status of pregnant minors in most states. Some adolescents may not be aware of their confidentiality rights and need information in this regard.

Patience is a second communication prerequisite, as repeated explanations and suggestions may be needed, depending on levels of anxiety and immaturity. Communication must be geared to emotional and intellectual development.[3] Adolescents aged 11 to 14 may have difficulty associating present actions with future consequences and need explicit guidance in the realities of pregnancy and parenthood. Adolescents aged 14 to 17 are preoccupied with asserting independence, and their rebelliousness can elicit defensiveness against health care professionals, which is to be avoided.[21] Because adolescents are concerned with peer approval, scenarios involving a "hypothetical friend"—If you had a friend who was pregnant, what would you tell her?—may be a useful strategy. Older teenagers aged 17 to 19 use more adult reasoning and can be treated as adults, but they can revert to immature thinking during the crisis of an unplanned pregnancy.[21,22]

Open communication is also more likely if a physician is perceived as nonjudgmental. Authoritarianism and imposing of personal views on issues such as abortion or unwed parenthood are counterproductive. A physician must be willing to recognize that adolescent sexuality and pregnancy are not inherently deviant behaviors and that teenage childbearing is not necessarily negative. Adverse medical and psychosocial consequences are distressingly frequent, but are not inevitable or even typical.[12] A longitudinal study of Baltimore teenagers points to a diversity of outcomes, with many teenage mothers—mostly black, inner-city residents—able to complete high school, find employment, and move off welfare, and many of their offspring making substantial progress toward independent adulthood.[23] A supportive social network, including but not limited to parents, male partners, and blood relatives, the adolescent's own capacity for interpersonal ties, her previous educational achievement, and having high future aspirations all predict successful teenage childbearing regardless of socioeconomic circumstances.[15]

There is, however, much heterogeneity, both within and between sociodemographic groups, in familial and cultural attitudes regarding teenage pregnancy and parenthood. A physician must therefore explore a teen's family and social environment without stereotypic preconceptions. Such an appraisal is key to assessing risks and to establishing dialogue around the emotionally laden and often threatening issue of family involvement. Family and social support promotes earlier care and improved clinical results for both abortion and childbearing and should be encouraged whenever possible.[17,24] On the other hand, disclosure may lead to rejection or abuse by a teen's family of origin. Problems are compounded if the adolescent pregnancy is symptomatic of family dysfunction.[25,26] In families that repress personal growth, a teenager's pregnancy may be her means of asserting independence. In others, the teen pregnancy may have diverted attention from more distressing conflicts and may have been tacitly encouraged. Familial substance abuse and violence, including possible sexual abuse, are also more likely to be present.[27] These issues may necessitate a referral to mental health care, perhaps urgently if there is concern about the patient's physical safety in disclosing the pregnancy. Nonthreatening and open-ended questions such as these, based on Smilkstein's Family APGAR, may help initiate discussions:[28]

- Do you enjoy being with your family?
- Can you turn to your family when something is bothering you?
- Can you talk to your family?
- Does your family get upset when you try something new?
- Does your family get upset if you express strong feelings?

When a Teenager Considers Abortion

A newly pregnant teenager must decide whether to continue the pregnancy. Such decisions are difficult regardless of age, but for teenagers, lack of information poses additional difficulties.[29] Some teenagers need clarification regarding the legality, availability, and timing of abortion. Although concerns about safety will remain, the medical risks of first-trimester terminations for teenagers are generally low.[30] Fever, hemorrhage, and emergency

abdominal surgical procedures occur in 1 to 2 per 1,000 teenagers undergoing first-trimester abortions. These rates are slightly lower than those for older women, and the teen mortality rate of 1.3 per 100,000 procedures is approximately half that of adults. The rate for cervical injury, which could affect subsequent childbearing, is 5.5 per 1,000 procedures among teenagers, notably higher than the rate for adults of 1.7 to 3.1 per 1,000. Fears about abortion-related emotional trauma are generally unfounded.[29]

All other options—parenthood or adoption—should be examined to ensure a complete appraisal.[8] The effect of a teenager's decision on her education or job plans should be discussed so that her choice supports her long-term goals. The risk of unsupported single parenthood or a premature, often unsuccessful, marriage should be explored as well. Most research indicates that teenagers older than age 15 have sufficient maturity for these assessments.[26,31] The advice of family and physician are important, but the decision should not be externally imposed. Careful consideration and ownership of the decision can offer a sense of personal control that promotes successful adjustment and encourages responsible sexual behavior.

Childbearing and Beyond

Childbearing teenagers need prenatal care, which can avert much of the risk associated with adolescent pregnancy.[4] Nonetheless, half of teenagers start prenatal care in the second trimester, 10% in the third trimester, and 2.4% receive no prenatal care.[32] For teenagers, the most salient reasons for this delay include denial, persisting family concerns, fear of labor and delivery, financial barriers, not knowing where or how to get prenatal care, and not appreciating its importance.[17] Black teenagers are more likely to delay seeking care than other racial and ethnic groups, a tendency that is not fully explained by differences in access to care.[33] Studies among nonobstetric groups of adolescents and among adults point to racial and ethnic differences in health-related attitudes and beliefs, which, among African Americans, may include untapped dissatisfaction with previous health care, a lower perception of the efficacy of health care or the seriousness of a given condition, and a tendency to seek help from family first.[34-36] Physicians should be aware of racial and ethnic differences in the use of health care and adjust counseling strategies as understanding of these differences increases.

Other counseling interventions include discussing a patient's fears about childbirth and addressing any misconceptions. When family insurance coverage is lacking, a physician may need to make suggestions as to where and how to apply for Medicaid or other available assistance. Providing information on which facilities serve teenagers who are pregnant and details on transportation, hours of operation, and how to obtain appointments can help increase teenagers' access to care.

Screening for gonorrhea, chlamydia, and bacterial vaginosis should be considered, especially if there is a long wait before a prenatal visit can be scheduled.[16] These infections may cause premature labor that earlier treatment can prevent. Perhaps most important, the value of prenatal care should be emphasized.[17]

Peer opinion is important in determining the attitude of teenagers. Discussing the experiences of friends is a means of assessing beliefs concerning prenatal care and identifying those teenagers unlikely to seek it in a timely fashion.[37] Follow-up telephone contact with some patients may encourage care that would otherwise be delayed or foregone.

A pregnant teenager's long-term plans should also be discussed. For some patients, information about adoption may be appropriate. Those teenagers who will keep their infants—95%—must answer a number of complex questions:

- Where will you live?
- Will you stay in school?
- Who will help you take care of your baby?
- Will the baby's father be involved? How about your parents or his family?
- Where will you and your baby get health care?
- How will you handle money?
- How soon do you plan to have another baby?

Visits for immunizations and infant health care may provide an opportunity for continuing these discussions after the baby is born.[4] Screening for maternal depression is important because expectations of parenthood may be dashed by the realities of caring for an infant.[4] The 20-item Center for Epidemiologic Studies depression scale is a valid screening tool for adolescents, with scores higher than 22 suggesting a clinically significant disorder and the need for further assessment.[38,39] Parenting programs can provide essential skills for teenaged mothers, and information on day-care services may enable them to continue their education. Contraceptive guidance is perhaps most important, however, as closely-spaced subsequent pregnancies strongly predict a truncated education, limited vocational skills, single parenthood, and long-term disadvantage.[2,9,11]

Conclusion

Teenage pregnancy and childbearing are embedded in our social fabric and will remain health care concerns. When pregnancy has already occurred, physicians can help teenagers reach sound decisions concerning pregnancy resolution and seek timely health care appropriate to those decisions. The communication methods outlined here can be adapted to the care of adolescents regardless of sex or gestational status and need not be limited to a reproductive context.

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Articles

Improving Cross-cultural Skills of Medical Students Through Medical School-Community Partnerships

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Postulating that a program integrating language skills with other aspects of cultural knowledge could assist in developing medical students' ability to work in cross-cultural situations and that partnership with targeted communities was key to developing an effective program, a medical school and two organizations with strong community ties joined forces to develop a Spanish Language and Hispanic Cultural Competence Project. Medical student participants in the program improved their language skills and knowledge of cultural issues, and a partnership with community organizations provided context and resources to supplement more traditional modes of medical education.

(Nora LM, Daugherty SR, Mattis-Peterson A, Stevenson L, Goodman LJ: Improving cross-cultural skills of medical students through medical school-community partnerships. West J Med 1994; 161:144-147)

Many health care professionals lack important knowledge about the minority cultures that they serve. Although some teaching models and specific programs designed to improve professionals' ability to deal with diverse patient populations have been developed, the programs are neither widely publicized nor generally available.[1,2] Some programs train people in foreign languages; others address cultural sensitivity generally; still others train health care professionals about the needs of specific minority groups.

We postulated that a program integrating language skills with other aspects of cultural knowledge was critical for developing skills, attitudes, and behaviors of medical students necessary to improve this health problem. We further postulated that a partnership with the targeted communities was a key factor in the development of an effective program.

Rush Medical College faculty worked with representatives of the Hispanic Health Alliance, a community-based organization in Chicago, Illinois, and the Center for Global Education of Augsburg College in Minneapolis, Minnesota, an organization with a strong presence in central Mexico, to develop a Spanish Language and Hispanic Cultural Competence Project to improve the medical Spanish language skills and enhance Hispanic cultural awareness of undergraduate medical students.

The reasons for concentrating this program on Spanish language and Hispanic cultures were as follows:

- Hispanics are the fastest-growing minority population in the United States. Currently numbering more than 20 million persons, the Hispanic population is expected to increase to more than 30 million persons by the year 2000.[3]
- Many factors work against Hispanic persons, particularly recent immigrants, receiving the best possible medical care. Disease prevalence and presentations differ from those of the majority population.[4-6]
- Language can be a barrier—many Hispanics speak only Spanish. Cultural beliefs, values, and health practices may also affect access to, participation in, and, ultimately, benefit from care.[7-9]
- Linguistic and cultural barriers are further complicated by the frequent perception of Hispanics as a single group.[5] Despite a common language, Hispanics represent a variety of cultures. These heterogeneous populations differ in health problems and practices as well as in cultural systems. To be effective, interventions must be geared to specific populations;[10]
- The lack of Hispanic health care professionals is another barrier to receiving the best medical care. The number of Hispanic medical students and physicians is not proportional to the size of the population.[12,13] Although the need to increase the number of Hispanic medical students and physicians has been recognized, and intensive efforts to accomplish this are underway, it is unlikely that there is a short-term solution.[11-13] Therefore, all medical

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students and physicians must be prepared to provide medical care to Hispanic persons in a way that is culturally competent.

Program Description

The Spanish Language and Cultural Competence Project has three component parts. The first is Spanish language training. Curricular blocks of 20 hours are offered in weekly two-hour class sessions, concentrating on medical terminology and physician-patient conversation. Additional informal Spanish conversation groups, led by bilingual volunteer faculty, are offered to reinforce classroom activities.

The second component, cultural competence training, also consists of 20-week curricular blocks offered in weekly two-hour sessions. This training includes didactic and small group sessions led by community experts who discuss a variety of topics. Demographic data, including geographic and regional differences in Hispanic populations, are provided, with particular emphasis placed on local demographics. Cultural differences between Hispanics and Anglo-Americans, the heterogeneity of the Hispanic community, and implications for health care are discussed. Nutrition, the acquired immunodeficiency syndrome, the status of women, traditional healing practices, and necessary skills for using interpreters are examples of class topics. Some classes involve excursions into the community.

A course syllabus, developed by the Hispanic Health Alliance, is provided to all attendees. In addition, supplemental materials are distributed by course faculty. By the end of each course, students have copies of articles, bilingual patient information sheets, and other materials that they can refer to in the future.

The third program component is an international seminar exploring issues of health care in a developing Hispanic country. The pilot eight-day experience was offered in June 1992. This experience afforded students an intensive learning experience concentrating on health policy and health practices in rural and urban areas of Mexico.

Students had a variety of experiences in Mexico. They planned and shopped for a meal using the average daily wage of a Mexican worker. They met with and observed practicing physicians, lay health promoters, and traditional healers. Students toured private and government-run hospitals, comparing these settings with those in the United States. Most important, students met with the citizens of Mexico—government officials, middle-class Mexican families, and indigenous peoples—and learned the health care situation from these perspectives. The importance of the social context of health care was emphasized through exposure to Mexico's culture and history and concerns related to its underdeveloped status, political system, and indigenous groups.

Local programming was the result of a partnership between the medical college and the Hispanic Health Alliance. The Hispanic Health Alliance is a nonprofit, community-based organization founded in 1983 and dedicated to improving the health status of Hispanics in Chicago. The alliance accomplishes its mission, in part, through the Provider Education Project, which is designed to improve the language skills and cultural awareness of health care professionals. Language curriculum had been developed by the Provider Education Project. The coordinator of that program and a medical school representative worked together to develop the cultural competence curriculum.

The local curriculum used the resources and talents available through Hispanic groups and agencies in the Chicago area. In this way, Hispanic community members acted as the primary faculty in the cultural competence portion of the course. In addition, students had the opportunity to visit several ongoing projects addressing the needs of local groups.

International programming was developed by the medical college in partnership with the Center for Global Education at Augsburg College. Founded in 1982, the center has a commitment to provide experiential education programs that expand people's world view and deepen their understanding of issues related to global justice. A unique aspect of the center's work is that participants have the opportunity to learn from the disenfranchised and poor of the region studied as well as the decision makers.

The center maintains on-site staff and facilities in Mexico. It provided pertinent pretrip and posttrip background materials and coordinated local programming in Cuernavaca and surrounding areas of Mexico. The programming was developed by a medical school representative working with the center's staff. Through the partnership, the center developed new programming, and medical college participants were able to benefit from experiences that would have otherwise been impossible.

All program components were available to students in good standing in the medical college. Total costs of the local programming were about $3,000. Course participants were asked to contribute $80, although need-based assistance was available. The medical college underwrote the remaining costs. Costs of the international seminar were $1,200 per participant. On average, participating medical students contributed 60% of the cost; substantial scholarship assistance was made available through two private donors and the Kellogg National Fellowship Program.

Cultural competence training was the only required component for all students involved in any aspect of the project. No student was permitted to limit participation to language training. This requirement evolved from a strong conviction that language training without cultural competence has the potential to do more harm than good; others concerned with the language and cultural competence have also presented similar concerns.[14] This component was so successful that it has since been opened to the entire university community.

Program Evaluation

Participants in the medical Spanish language part of the project completed pre- and postcourse written tests of

Spanish into English and English into Spanish translations. This test had been previously developed and used by the language teacher as an assessment instrument for health care practitioners learning medical Spanish.

Cultural competence component participants and a control group of nonparticipants completed tests of knowledge of Hispanic health and cultural issues before beginning and near the end of the session. This test consisted of multiple-choice questions about disease prevalence, demographics, cultural perceptions, and traditional health practices of Hispanic communities. The test had been developed by our community-based organization partner and used previously to evaluate Hispanic cultural knowledge of physicians and other health care workers.

Participants and the control group also completed the misanthropy scale of Sullivan and Adelson.[15] This scale modifies the ethnocentrism scale used by the University of California public opinion study and replaces reference to specific minority groups with more general wording. The test was used to measure general openness to those not like oneself. We included the misanthropy scale to help assess if students participating in such a program were more likely to be open toward other groups than nonparticipants and whether a course focused on a specific ethnic population could increase sensitivity to groups beyond the population studied. All participants attended discussion sessions. In addition, participants in the international seminar completed questionnaires specifically geared toward that experience.

Results

Local Programming

In the combined language-cultural knowledge program, 19 students began the course; an additional 4 students began cultural competence training. Common reasons for nonparticipation, despite initial interest, included time constraints and financial pressures. A total of 15 students completed the combined training. Reasons for discontinuing included academic difficulties (one student), dissatisfaction with language instruction (one student), and competing time demands from simultaneous required clinical clerkships (two students). Most participants were preclinical students, with time constraints a frequent reason given for nonparticipation of students in the third and fourth years of training.

Spanish language skills showed notable improvement as a result of the course. Test scores changed from an initial average of 60% to a posttest average of 75% proficiency. Some students had a dramatic improvement; one student raised her precourse score of 13% to a postcourse test score of 54% proficiency.

Testing of cultural knowledge also suggests a benefit of the course. For the control group, average precourse scores were 46% and postcourse, 42%. The participant group averaged 40% precourse and 58% postcourse. While control group scores did not change from pretest to posttest, course participants showed a significant improvement (paired comparison $t = 3.10$, $P = .007$).

Misanthropy scale results revealed no differences between course participants and the control group at the outset. Postcourse results show a trend, although nonsignificant, toward an increase in general acceptance of others in course participants compared to control group members. The small number of persons tested provides only limited power for this comparison and may account for the nonsignificant results.

Course discussion sessions provided important qualitative information not available through the testing. One student with no precourse Spanish language ability described being able to assist a Spanish-speaking woman during labor and childbirth as a result of her new skills. A second student detailed how the course helped her to recognize and intervene when inadequate language interpretation occurred in a clinical situation. Examples such as these offered inspiration to the entire participant group as well as to faculty. Many students noted the value of going into the community during the course. Students were enthusiastic about the course and its continuation.

International Seminar Component

In the international seminar, 11 persons, including 8 medical students, took part. Most students were at the end of their second year of medical school and preparing to begin clinical work. Of the 8 medical students, 6 were women. The most common reason for nonparticipation, despite initial interest, was a lack of financial resources. Some form of scholarship assistance was given to 7 students.

All students completed anonymous surveys. The respondents were uniformly positive about the experience, and all said that the seminar far exceeded their expectations. Two respondents had some concern about the intense scheduling, which included several 15-hour days, but could not identify any experience that they would eliminate or shorten.

Comments from these surveys and postseminar follow-up sessions are enlightening. Several students noted that experiencing the health issues of potable water, plumbing, and infrastructure firsthand was dramatic. The opportunity to meet with Mexicans, including indigenous persons, in their homes was an eye-opener for many. More than one student expressed awe in the presence of a traditional healer when she discussed various methods of diagnosing and treating health problems. In comments six months after the trip, four participants characterized the seminar as a life-changing experience.

Discussion

Several areas of knowledge are important for providing culturally competent health care. Specific information about disease prevalence and presentation in various populations must be known. Basic language skills, including medical terminology, may be useful. Scientific knowledge and language skills are inadequate by themselves, however.

Health care professionals should understand the effect that different language and nonverbal communication patterns, explanatory models of disease, and contextual fac-

tors may have on the expectations of patients and their perceptions of the behavior of physicians.[14-16] An appreciation of cultural practices and possible ways to incorporate them into medical treatment can further enhance health care delivery.

The Spanish Language and Cultural Competence Project demonstrates a way to improve language skills and cultural competence in undergraduate medical students. This study shows that many medical students wish to enhance their language and cross-cultural skills and are willing to devote substantial energy toward doing so. Four hours per week of scheduled time is valuable for any person and particularly so for medical students. Most language training does require a regular and substantial commitment of time, however. Most students completed the program despite competing demands on their time. We see this as a testament to the perceived need and dedication of the students. This impression is supported by the number of students who attended (and requested additional) informal conversation groups.

Language skills and cultural knowledge were assessed using written examinations. Written tests may not adequately evaluate students' ability to communicate with Spanish-speaking patients. Although students noted that patient encounters were improved with their developing language skills, other methods of testing oral communication abilities are needed. We plan to develop simulated patient experiences to reinforce and evaluate language skills and other challenges faced by clinicians treating patients from another culture.

Course participants showed improvement in their cultural knowledge after the course compared to a control group. We think that the degree of improvement shown is what might be expected given the length of the program.

Our initial concern that students volunteering for a cultural awareness program might be those that least needed such a course was not supported by study results. Course participants and those who opted not to participate were equally tolerant at the beginning of the experience. On the other hand, there is a suggestion that the experience improved the tolerance of participants toward other groups. If further study supports this conclusion, an important implication may be that cultural competence programs directed toward one group may improve acceptance of persons across multiple other groups.

Two aspects of this program are particularly important. Cultural competence training was required of all participants. We thought that language training without associated cultural training could ultimately work against providing the best training and patient care. Second, the program was developed in partnership with community-based representatives. We thought that cultural competence training would be enhanced by having the community participate in designing and implementing the program.

Using community expertise was, in fact, critical to the cultural competence programming at the local and international levels. Partnership with a community-based organization helped identify issues to be addressed and facilitated access to the community in a nonvoyeuristic fashion. Community experts provided insights that students would not have obtained from course readings or noncommunity-based speakers.

Working with community members presented certain challenges as well. Comfort with the teaching role varied among community experts. Instruction style frequently varied from that typically found in the medical school setting. Questions and comments from course participants were sometimes unwittingly insensitive. The tolerance and sense of humor that most local experts exhibited as they responded to insensitive remarks were extremely effective models for medical students hoping to perform credibly in cross-cultural settings.

Participants in the international seminar benefited from the trust that the local people placed in the local organizers and their willingness to extend this trust to our students. This was particularly important in the case of the indigenous and marginal communities visited. Without these previously established relationships, it is unlikely that our medical students would have had the opportunity to meet with a practicing traditional healer or to discuss personal medical histories with local residents.

Our study shows that medical students' ability to care for diverse patient groups may be enhanced by programs that link language study and training in cultural competence. Traditional modes of medical education are improved by community partnerships that provide an important context and resources to the student experience. As a result, medical students may be more adept at overcoming barriers present in multicultural situations, and the quality of health care provided to all populations can be improved.

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Conferences and Reviews

Clinical Aspects of *Campylobacter jejuni* Infections in Adults

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***Campylobacter jejuni* is an almost ubiquitous, microaerophilic, gram-negative rod. Outbreaks have been associated with drinking raw milk or contaminated water and eating poultry. *Campylobacter jejuni* accounts for 3.2% to 6.1% of cases of diarrheal illness in the general population of the United States, and infected patients frequently present with abdominal pain and fever. Less frequently, *C jejuni* is responsible for bacteremia, septic arthritis, septic abortion, and other extraintestinal infections. Reactive arthritis, Reiter's syndrome, the Guillain-Barré syndrome, and pancreatitis may accompany or follow *C jejuni* enterocolitis. *Campylobacter jejuni* is an important cause of diarrheal illness and is a more commonly identified stool organism than *Salmonella* or *Shigella* species. Recurrent and chronic infection is generally reported in immunocompromised hosts.**

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Campylobacter jejuni is a common cause of enterocolitis. In this article I review the clinically relevant features of this frequent but often unrecognized cause of disease. In scope, this review is limited to *C jejuni* and *Campylobacter coli* infections in adults. I review the microbiology, epidemiology, manifestations, diagnosis, and treatment of the disease.*

Methods

Relevant articles were identified through a MEDLINE search from 1981 to early 1993 and from bibliographies of the selected articles. Articles selected for detailed review included original research articles, review articles, book chapters, and letters related to *C jejuni* and *C coli* infections in adults. A total of 312 articles were reviewed in detail. The reproducibility of methods for extracting data and selecting articles for this review was not assessed, but the results are similar to those of older published reviews.

Microbiology and Taxonomy

The word "campylobacter" is derived from the Greek *campylo* ("curved") and *bacter* ("rod"). *Campylobacter* species are slender, spirally curved, gram-negative rods. They have a characteristic corkscrew-like, darting motility by means of a single polar flagellum at one or both ends. *Campylobacter* species are, in general, microaerophilic and require oxygen concentrations of 3% to 15% and carbon dioxide concentrations of 3% to 5%. They produce catalase but do not ferment or oxidize carbohydrates.[1]

The campylobacters were originally classified with members of the genus *Vibrio* as *Vibrio fetus*. In humans, the current *Campylobacter fetus* is most commonly a bloodstream isolate associated with a febrile illness,[2] but it has been associated with such illnesses as thrombophlebitis, endocarditis, infected aortic aneurysm, septic arthritis, and osteomyelitis. In 1957 a subgroup of *Vibrio fetus* was described that was called the "related vibrios," which grew at 37°F and 42°F but not at 25°F, unlike *V fetus*, which grew at 25°F and 37°F but not 42°F.[3] In 1973 *V fetus* and the "related vibrios" were reclassified into the genus *Campylobacter* based on differences from the vibrios in the guanine and cytosine content and cell membranes.[4]

Of the thermotolerant campylobacters, *C jejuni* and *C coli* have been recognized as the most important causes of human disease. *Campylobacter jejuni* is a common cause of enteritis in humans; it almost always hydrolyzes hippurate in the laboratory. *Campylobacter coli* also causes human disease but is also frequently identified in swine and does not hydrolyze hippurate. *Campylobacter pylori* was recently reclassified into the genus *Helicobacter;* a number of other *Campylobacter* species have been described and are discussed elsewhere.[5]

For the purposes of this review, *C jejuni* and *C coli* will be referred to collectively as *C jejuni* unless otherwise specified because their clinical manifestations are similar and many earlier reports in the literature did not differentiate between the two species.

Epidemiology

Campylobacter jejuni is the cause of 3.2% to 6.1% of cases of diarrheal illness in the general population of the United States,[6-12] whereas species of *Salmonella* represent 2.1% to 3.6% and those of *Shigella* 0% to 2.9% of cases

*See also the editorial by B. Mishu, MD, and M. J. Blaser, MD, "Do You Have a *Campylobacter* in Your Future?" on pages 186-187 of this issue.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
Ig = immunoglobulin

of similar illness.[8-12] Similar *C jejuni* isolation rates have generally been noted in Canada, Great Britain, Belgium, Australia, the Netherlands, and Sweden, although several series from developed countries have reported isolation rates of greater than 10% in patients with diarrheal illnesses.

Campylobacter jejuni is an important cause of travelers' diarrhea, accounting for 5.8% to 15.2% of cultured cases. It is infrequently identified in healthy controls in developed countries, but it was identified in stool specimens of 14.8% of healthy persons without diarrhea in southern India.[13]

A bimodal curve describes the age-specific isolation rate of *C jejuni,* with infants and young adults having the highest age-specific rates of isolation. In most series, rates of infection are highest in the summer months.[14,15] Most sporadic cases probably result from ingesting contaminated foods (such as poultry),[14-16] drinking raw milk,[9,16] drinking untreated water,[16,17] or contact with animal reservoirs.[15,16]

Campylobacter jejuni has been isolated from both fresh water and seawater, and several outbreaks of *C jejuni* enteritis have been associated with drinking contaminated water, including a large outbreak in Bennington, Vermont, in 1978 involving 2,000 to 3,000 people.[18]

Outbreaks have also been traced to unpasteurized[19,20] and improperly pasteurized milk. In some instances, *C jejuni* has been identified in rectal swabs of implicated dairy cattle[19,20] or from milk-processing equipment at an implicated dairy. Raw goat's milk has also been identified as the source of an outbreak. The consumption of cake (or cake icing), eggs, and beef has been associated with illness in a few outbreaks.

Outbreaks of *C jejuni* enteritis have been associated with the consumption of chicken and turkey. The handling of raw poultry has also been linked to human infection. Between 68% and 91% of live chickens and nearly 100% of commercial turkeys carry *C jejuni.* Cultures have been positive in 33% to 43% of poultry carcasses and 23.1% to 36% of retail chicken specimens. In contrast, *C jejuni* was cultured from only 1.6% of a large sampling of pork, beef, and lamb specimens at abattoirs and retail outlets.[21]

Less frequently, contact with dogs and cats has been reported as a source of infection in humans. In one study, 3,068 fecal, caecal, intestinal, and rectal specimens from animals were tested, and *C jejuni* was found in 66% of hogs, 43% of cattle, 23% of sheep, 35% of ducks, 17% of pigeons, 10% of other birds, 13% of dogs, 6% of hoofed zoo animals, and only 4% of reptiles.[22]

Person-to-person transmission is reported but appears to be infrequent.[14,18] In one case, laboratory-acquired *C jejuni* enteritis developed after a broth culture was accidentally spilled.[23] A case of "post-transfusion septicemia" developed in a patient with Waldenström's macroglobulinemia after he received blood from a person with serologic evidence of recent *C jejuni* infection.[24]

Clinical Manifestations

Enterocolitis

The common manifestations of *C jejuni* enterocolitis are presented in Table 1. Most frequently there is a self-limited diarrheal illness with associated abdominal pain that may be severe. Malaise, fever, anorexia, headache, nausea, vomiting, myalgia, and grossly bloody stools may also be present.[6,10-12,15,18-20,25-32] The diarrheal illness is similar to the enteritis caused by *Salmonella* or *Shigella* species. Death in association with *C jejuni* enteritis is rare.[33]

In experimental situations, infection has occurred after as few as 500 organisms were ingested.[34] The mean incubation period was estimated in one study to be 68 hours[29] and in another was 4 days.[35] The mean duration of excretion has been reported as 10.1 days,[36] and the duration of excretion is almost always less than 6 weeks in untreated subjects.

On presentation, some cases of *C jejuni* infection are indistinguishable from those of ulcerative colitis[6,30,37] or Crohn's disease,[6] and the illness has presented as a massive lower gastrointestinal tract hemorrhage. A number of patients have been taken to surgery because of abdominal pain with presumed appendicitis; only rarely has the appendix been inflamed and *C jejuni* thought to be the causative organism, however.[38,39]

The pathogenesis of *C jejuni* on the gut mucosa is incompletely understood. Some strains of *C jejuni* have been shown to produce a variable amount of enterotoxin that has similarity to the cholera toxin, but the pathogenesis of *C jejuni* on the gut mucosa is probably caused in large part by bacterial invasiveness. Immunohistochemical and ultrastructural evidence of invasion into the colonic mucosa has been found in a series of 22 patients, and an increased number of immunoglobulin (Ig) A- and IgM-containing plasma cells were noted in the colonic mucosa of infected patients.[40]

TABLE 1.—*Common Manifestations of* Campylobacter jejuni *Enteritis**

Symptom or Sign	*Patients Affected, %*
Diarrhea	75-100
Abdominal pain or cramps	55-97
Malaise	73-95
Fever	52-91
Anorexia	83-90
Headache	12-82
Nausea	30-76
Chills and sweats	29-75
Myalgia	19-69
Vomiting	19-55
Gross blood in stool	6-57

*From Drake et al,[6] Blaser et al,[10-12] Deming et al,[15] Vogt et al,[18] Taylor et al,[19] Komblatt et al,[20] Stehr-Green et al,[25] Mentzing,[26] Tiehan and Vogt,[27] Porter and Reid,[28] Korlath et al,[29] Goodman et al,[30] Nolan et al,[31] and Gray and Pedler.[32]

On radiologic examination of patients with enteritis, findings vary from normal small bowel or colon to edema and ulceration of the small bowel and of the colon.[37,41,42] On sigmoidoscopy, there may be mucosal edema, exudate, granularity, and contact bleeding.[42-46] The findings of a rectal biopsy may be normal[40,44] or mimic ulcerative colitis, but most cases have histologic features of a nonspecific infectious colitis.[40,43,44,46,47]

Immunocompromised patients appear predisposed to chronic or recurrent *C jejuni* enterocolitis. Recurrent or chronic infection has been reported in patients with hypogammaglobulinemia and in persons with the acquired immunodeficiency syndrome (AIDS). Not surprisingly, a blunted or impaired antibody response to *C jejuni* has been noted in patients with recurrent or persistent infection.[47-49]

Other Gastrointestinal Manifestations

In a few cases, *C jejuni* has been isolated from the bile of patients who have undergone surgical therapy for cholecystitis. Acute pancreatitis has also been occasionally associated with *C jejuni* enteritis. The pathogenesis of acute pancreatitis associated with *C jejuni* enteritis is not understood, but as mentioned with the cases of cholecystitis, *C jejuni* can be found in the biliary tree of some patients.

Campylobacter jejuni has been reported as the cause of spontaneous bacterial peritonitis in a patient with cirrhosis and massive ascites due to alcoholism.[50] In one study, six of the authors' patients and seven others from the literature had *C jejuni* or *C coli* peritonitis associated with continuous ambulatory peritoneal dialysis.[51] These patients frequently had associated diarrhea that preceded the peritonitis in some cases.

Bacteremia and Recurrent Illness

Although a number of reports describe bacteremia in patients with *C jejuni* infection, bacteremia is generally not reported. In a summary of 8,320 human cases of infection with *Campylobacter* species, it was noted that only 0.4% of *C jejuni* isolates were from blood whereas 63% of *C fetus* isolates were from blood.[2] Others have shown in vitro that *C jejuni* is sensitive to normal human serum with an intact complement pathway whereas *C fetus* is relatively resistant.[52]

In normal subjects with *C jejuni* enterocolitis, serum IgA, IgM, and IgG antibodies to *C jejuni* rise during the second week after infection. A number of the reported cases of *C jejuni* bacteremia have occurred in immunocompromised patients such as persons with hypogammaglobulinema, recipients of corticosteroid therapy, patients with AIDS, and patients with malignant neoplasms. Bacteremia is substantially more common in AIDS patients with *C jejuni* infection than in otherwise healthy controls with *C jejuni* infection,[53] and several authors have noted that most cases of extraintestinal infection with *C jejuni*, including bacteremia, occur in patients at the extremes of age.

Rheumatic Manifestations

As much as 3% of cases of *C jejuni* enteritis may be followed by Reiter's syndrome or by a reactive arthritis.[54] The reactive arthritis is similar to that which follows venereal infection with *Chlamydia trachomatis* or enteric infection with *Shigella flexneri, Shigella dysenteriae, Salmonella typhimurium,* or *Yersinia enterocolitica.* The reactive arthritis associated with *C jejuni* is usually an oligoarticular arthritis that is asymmetric and most frequently involves the knees, ankles, or wrists.[54] The mean interval between the start of the enteritis and the arthritis is ten days.[54]

Campylobacter jejuni infection has only rarely been reported as the cause of septic arthritis, osteomyelitis, or prosthetic joint infection, and these cases all occurred in compromised hosts.

As listed in Table I, nonspecific myalgias occur in 19% to 69% of cases of *C jejuni* enteritis.[26-32]

Neurologic Manifestations

An association is increasingly seen between *C jejuni* infection and some cases of the Guillain-Barré syndrome. In 1982, a case of the Guillain-Barré syndrome occurred in a 45-year-old man two weeks after an episode of culture-proven *C jejuni* enteritis.[55] Since then, a number of such cases have been reported in adults. These reports include several variants of the Guillain-Barré syndrome, and the severity of disease varies greatly.

In a series of 106 patients with the Guillain-Barré syndrome, 4 patients had known *C jejuni* infection preceding the development of their disease.[56] In a retrospective study of 56 Australian patients with the Guillain-Barré syndrome, 38% were noted to have serologic evidence of preceding *C jejuni* infection, but there was no evidence of previous infection in 27 control patients with other neurologic disorders or in 30 healthy controls.[57] More recently, it was reported that serologic evidence of recent infection with *C jejuni* was considerably more frequent in a series of 118 patients with the Guillain-Barré syndrome than in 56 controls with other neurologic diseases or in 47 healthy controls.[58] Finally, of 46 patients with the Guillain-Barré syndrome, 19 (41%) had evidence of *C jejuni* infection, and the majority of the *C jejuni* organisms identified in these patients belonged to Penner serogroup 19.[59]

The relationship between cases of the Guillain-Barré syndrome and preceding *C jejuni* enteritis is not well understood. High titers of IgG against GM_1 ganglioside were reported in two patients with acute axonal polyneuropathy following *C jejuni* infection, although no elevation of anti-GM_1 antibodies was noted in a subsequent but less severe case. Other investigators found that the serum of a patient who acquired the Guillain-Barré syndrome after *C jejuni* enteritis reacted to PO myelin-specific protein.[60]

Campylobacter jejuni meningitis has been reported in an adult who had previously undergone craniotomy for neuroblastoma. The illness was successfully treated with chloramphenicol.

Dermatologic Manifestations

An erysipelas-like cellulitis from *C jejuni* has been reported in three patients with hypogammaglobulinemia

and recurrent *C jejuni* bacteremia,[61] and cellulitis was reported in a patient with Bruton's (X-linked) agammaglobulinemia and in a patient with vascular disease.[62] Erythema nodosum is occasionally reported in patients with *C jejuni* enteritis.

Septic Abortion and Miscarriage

Campylobacter jejuni has been isolated from fetuses and from maternal blood in cases of septic abortion as well as from maternal blood in cases of early miscarriage. A patient with agammaglobulinemia suffered recurrent abortions that were thought to be due to *C jejuni* infection.[63]

Other Manifestations

Myocarditis has been reported in association with *C jejuni* enteritis. In the reported cases thus far, the disease has been self-limited.

Cases of the hemolytic-uremic syndrome have rarely been associated with *C jejuni* infection in adults.

Campylobacter jejuni is a rare cause of urinary tract infection. Blaser and co-workers have noted that the survival of *C jejuni* is brief in urine at 37°F.[64]

Diagnosis

A presumptive diagnosis of *C jejuni* enteritis may be made on the basis of an appropriate history and the presence of darting organisms on phase-contrast microscopy of a fresh stool specimen.[7] Fecal leukocytes have been reported in 66%[6] to 100%[65] of fecal wet mounts, and erythrocytes are also frequently present on a wet mount of stool.[65]

Campylobacter jejuni may be isolated from stool by passing the stool specimen through a filter (0.45 μm Millipore filter), which removes larger bacteria present in the stool and allows the relatively small campylobacters to pass onto the medium, as originally described in 1972.[66] In 1977 the use of selective media for isolating *Campylobacter* species, which inhibits the growth of other bacteria and yeast, was described.[67] Other isolation media have been outlined and include Preston, modified CCDA,* and Butzler media.[68] One author noted a nearly twofold increase in *Campylobacter* isolation rates when using the filtration method rather than standard plating on selective media.[69] DNA probes have been developed for *C jejuni* and *C coli* that may become clinically important.

Serotyping has been epidemiologically useful in some outbreaks of *C jejuni* enteritis. Methods of serotyping *C jejuni* strains that rely on heat-stable and heat-labile antigens have been described.[70,71]

Therapy

Because *C jejuni* enterocolitis is generally a self-limited illness, most patients require no more than supportive treatment. Antimotility agents have been shown to impede the resolution of infection and to increase the need for antimicrobial therapy.[31] When antibiotic treatment is necessary, several authors have suggested erythromycin as the drug of choice for *C jejuni* enterocolitis. Most authors believe that erythromycin therapy does not alter the clinical course of enteritis caused by *C jejuni*; unlike with *Salmonella* species enteritis, antibiotic treatment shortens the fecal excretion of the organism rather than prolonging it.

Erythromycin resistance in *C jejuni* is chromosomally mediated and involves the alteration of ribosomes so that erythromycin binding is not favored. Resistance has been noted in 0.5% to 8.4% of organisms from developed countries; however, 65% of those isolated from a series in Thailand were erythromycin-resistant.[69] Erythromycin resistance is substantially more common with *C coli* than with *C jejuni*.

Campylobacter jejuni is usually sensitive to gentamicin, tetracycline, doxycycline, furazolidone, nitrofurantoin, and ciprofloxacin. Ciprofloxacin, gentamicin, doxycycline, and tetracycline have been suggested as alternative agents to erythromycin, but quinolone resistance has emerged. The role that newer macrolide drugs might play in the treatment of *C jejuni* infection is not yet known. Intraperitoneal aminoglycoside administration and oral erythromycin have been suggested for the treatment of *C jejuni* peritonitis associated with continuous ambulatory peritoneal dialysis.[51]

Preventive measures such as careful preparation and thorough cooking of poultry, pasteurization of milk, and chlorination of water are important in preventing infection with *C jejuni* and *C coli*.

Conclusions

Campylobacter jejuni and *C coli* are common causes of self-limited enterocolitis, which usually presents with diarrhea and abdominal pain. Outbreaks have been associated with the consumption of raw milk, surface water, and poultry. Extraintestinal manifestations such as reactive arthritis, Reiter's syndrome, pancreatitis, or the Guillain-Barré syndrome may occur with *C jejuni* infection, and recurrent or chronic infection may be found in immunocompromised patients. Erythromycin is regarded as the antibiotic of choice when supportive therapy alone is inadequate; erythromycin-resistant strains occur, however, and gentamicin or ciprofloxacin have been suggested as alternative agents.

*Modified CCDA is a selective blood-free agar base containing nutrient broth, charcoal, casein hydrolysate, sodium *d*esoxycholate, ferrous sulfate, sodium pyruvate, and *a*gar.

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Lead Poisoning

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Lead poisoning is the most common disease of environmental origin in the United States today. Adult lead poisoning results primarily from exposure by inhalation in the workplace. Pediatric lead poisoning results principally from the ingestion of lead from environmental media, including paint chips, dust, soil, drinking water, ceramics, and medications. Lead is toxic to many organ systems, among them developing erythrocytes, the kidneys, and the nervous system. Lead-induced toxicity to the central nervous system causes delayed development, diminished intelligence, and altered behavior. In young children, this effect has been demonstrated convincingly to occur at blood lead levels between 10 and 20 μg per dl. The Centers for Disease Control and Prevention has recommended that a blood lead level of 10 μg per dl or higher be considered evidence of increased lead absorption, and the National Academy of Sciences has concurred in that recommendation. Unresolved issues in need of further study include the frequency of screening young children for lead, the question of whether women should be offered screening for lead before conceiving a pregnancy, the role of x-ray fluorescence analysis in assessing lead in bone, and the appropriate legislative response of the United States government to lead-based paint abatement.

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Lead poisoning is the most common disease of toxic environmental origin in the United States today. It affects both children and adults. Lead is now known to be toxic to persons of all ages at levels that only a few years ago were considered to be safe. This realization has forced major revisions of strategies for the prevention and management of lead poisoning.[1,2]

In this article, we review recently developed information on the epidemiology and toxicology of lead exposure, particularly at low doses. In addition, we review recent research and current controversies in diagnosing and preventing lead poisoning.

Epidemiology and Sources of Exposure

Adult Exposure to Lead

Most adult exposure to lead occurs in the workplace. The usual route of occupational exposure is by inhalation. The potential for occupational exposure exists in hundreds of industries, and the National Institute for Occupational Safety and Health estimates that more than 3 million workers in the United States are at risk.[3] Industries classically associated with lead exposure include smelting, battery making, ship burning, soldering, stained glass manufacture, brass foundry work, and lead-based paint abatement. More recently construction and demolition work have become major sources of occupational lead exposure. Lead exposures in construction are intense, and although exposure to lead in most industrial sectors has been effectively controlled by standards promulgated by the US Occupational Safety and Health Administration (OSHA), construction work had until 1993 been exempted from those protections. Particularly severe exposures have occurred in construction workers involved in the demolition and renovation of painted steel structures such as bridges and elevated highways.[4,5]

Nonoccupational exposure to lead is also widespread in the adult population of the United States, but levels are generally lower than those in the workplace. Persons of all ages encounter lead in air, dust, soil, and drinking water.

Pediatric Exposure to Lead

Because of their normal oral exploratory behavior, children absorb most of their lead by ingestion.[6] The mean blood lead level in children in the United States today is about 5 μg per dl. This level is substantially higher than that found in preindustrial populations living in remote areas, but is substantially lower than that of American children in the mid-1970s, reflecting enormous decreases in the use of lead in gasoline.[7] An estimated 3 to 4 million American preschool children have blood lead levels above 10 μg per dl, a level now recognized to be associated with subclinical neurologic impairment.[6] Among poor, minority, inner-city preschool children, the prevalence of blood lead levels above 10 μg per dl is estimated by the Centers for Disease Control and Prevention to be as high as 68%.[8]

Lead-based paint. Lead-based paint continues to be

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the principal source of high-dose lead exposure for children in the United States. An estimated 57 million housing units in the United States contain lead-based paint, and in 3.8 million homes children are intimately exposed to deteriorating lead paint.[8]

Although lead-paint poisoning classically occurs among poor children living in deteriorated housing in inner cities, the disease does not respect geography or social station. Lead-paint poisoning has been reported in the children of affluent parents who have moved into cities as "urban homesteaders."[9] It has also been reported among children living in lead-painted houses in suburban and rural areas.[10] Household renovations are associated with particularly severe lead exposures.[9,10]

Children may absorb lead from paint directly by ingesting paint chips (pica), or they may absorb it indirectly by inadvertent ingestion of lead-contaminated house dust. The latter route is the more common.

Contaminated dust and soil. Contaminated dust and soil are pervasive sources of lead exposure for children.[8,11] Concentrations of lead in dust and soil range from near zero to many thousands of parts per million. In urban and suburban areas, the principal sources of lead in dust and soil are flaking paint from buildings and bridges, automotive emissions (much less now than a decade ago), and industrial releases. In general, lead in dust and soil appears to be responsible for elevations in children's blood lead levels when the lead concentration exceeds 300 to 500 ppm.[12,13]

Airborne lead. Airborne lead is generally a low-dose source of exposure for children.[8] Automotive and industrial emissions are the major contributors to lead in air. Automotive emissions have diminished substantially since the phasedown of lead in gasoline,[7] and industrial lead emissions have been reduced in most areas since the passage of the Clean Air Act.

Although industrial emissions account for only a small fraction of airborne lead releases to the air, these stationary sources can produce concentrated zones of extremely high-dose exposure. The worst such situation in the United States existed in the vicinity of a large lead ore smelter in Kellogg, Idaho. In 1974, 98% of 1- to 9-year-old children living within a mile of this smelter had blood lead levels greater than 40 μg per dl, and 22% had levels above 80 μg per dl.[14]

Drinking water. Drinking water is a common source of lead exposure.[8] Although lead is seldom present in drinking water in high concentrations, it contributes widely to background exposure across a wide segment of the American population. At its source drinking water is almost always lead-free but can become contaminated as it passes through lead pipes or comes into contact with lead solder. Aggressive soft water of low pH poses the greatest hazards because it has the highest potential of leaching lead from pipes and solder.

Leadworkers' children. Children of leadworkers may be exposed to lead dust transported home from the workplace.[15] In an evaluation of lead exposure among workers' children, a close correlation was found between children's blood lead levels, the severity and duration of parental exposure, and the lead concentration of household dust. Of 91 workers' children, 38 (42%) had elevated blood lead levels and 10 required treatment for lead poisoning.[15] Under regulations set forth in 1978 by OSHA, industries using lead are now required to provide changing and showering facilities for their workers.[16] Although this measure has greatly reduced the incidence of take-home lead poisoning, such poisoning is still seen occasionally among the children of construction workers, reflecting the exemption until August 1993 of construction work from OSHA protections.

Home remedies. Home remedies can occasionally be a source of lead poisoning in both adults and children. Numerous case reports have documented this hazard,[17,18] and it appears to be especially common among ethnically isolated groups.

Body Burden of Lead

The lead burden, the total amount of lead in the human body, represents the difference between the cumulative lifetime absorption of lead from all sources and total excretion.[19] Lead is not distributed homogeneously in the human body. Experimental studies have shown instead that it is dispersed among several physiologically distinct compartments that differ from one another in their size and accessibility. These compartments and their interrelations can be portrayed by metabolic models that describe both qualitatively and quantitatively the absorption, distribution, deposition, accumulation, and excretion of lead.

A reasonable portrayal of the functional anatomy of the body lead burden is provided by the model of Rabinowitz and co-workers.[20] This model is based on stable isotope and metabolic balance studies. It proposes that the lead burden be described in terms of three dynamically interrelated compartments.

Lead in Blood

Lead in blood makes up about 1% of the body lead burden in the Rabinowitz model. Because it is conveniently accessible and is the fraction of the body burden that correlates most closely with recent environmental exposures, it is the component of the body burden most frequently measured. Approximately 90% of the lead in blood is found in the erythrocytes. The half-life of lead in blood is 36 ± 5 days.

Lead may be added to the blood compartment by inhalation, ingestion, or movement from the deeper compartments. The influence of lead from the deeper compartments on the blood lead level is proportional to the amount of lead in those stores,[21] although there exists considerable interindividual variability in the release of lead from bony stores. If the amount of stored lead is large, its effects on the blood lead level can be considerable; conversely, if skeletal lead stores are small, then lead recently inhaled and ingested becomes the dominant factor determining the blood lead level. Thus, in the early phases of exposure to lead, the blood lead level rises rapidly and provides a sensitive indicator of recent ab-

sorption.[14,20,21] By contrast, in persons with long-term heavy exposures to lead, such as workers with many years' employment in the lead industries, the blood lead level has been found to correlate poorly with current exposure; under those conditions, the blood lead level appears principally to reflect the release of stored lead.[21]

Soft-Tissue Lead

Compartment 2 in the Rabinowitz model is composed principally of soft tissue lead.[20] Lead in soft tissues such as the kidneys, bone marrow, and nervous system is responsible for most of lead's toxicity.

Skeletal Lead

Lead in the skeleton is by far the largest component of the body burden.[20] This compartment contains about 99% of all lead in the human body. Skeletal lead is calculated to have a half-life of approximately 10,000 days.[20] Lead in the skeleton appears to exist in two physiologically distinct compartments. Lead in trabecular bone plus lead in the subperiosteal and subendosteal regions appears to constitute a relatively mobile fraction of the bone lead, whereas lead in deep cortical bone is relatively immobile.

Lead Poisoning

Lead is now well recognized to produce a wide range of toxicity. These toxic effects extend from acute, clinically obvious, symptomatic poisoning to subclinical effects.[1]

Acute Toxicity

Intense, acute exposure to lead, either by inhalation in the workplace or by the ingestion of paint chips among children, can cause acute symptomatic poisoning. Characteristics of this life-threatening syndrome are abdominal colic, constipation, fatigue, anemia, peripheral neuropathy, and in most cases, alteration of central nervous system function.[22] In severe cases, a full-blown acute encephalopathy with coma, convulsions, and papilledema may occur. In milder cases, only headache or personality changes may be evident.[22] In many instances, persons who have suffered from acute lead encephalopathy are left with permanent neurologic and behavioral sequelae.[23]

'Subclinical' Toxicity

Subclinical toxicity denotes the concept that relatively low-dose exposure to lead can cause harmful effects that are not evident on a standard clinical examination.[24] The underlying premise is that there exists a continuum of toxicity in which clinically apparent effects have their asymptomatic counterparts; these subclinical counterparts have recently been called "biologic markers" of toxicity.[25] Thus, clinically obvious manifestations of lead poisoning such as anemia, neuropathy, and renal failure lie at the upper end of the range, whereas such covert effects as impaired biosynthesis of heme, slowed nerve conduction, and altered excretion of uric acid are their subclinical correlates. It is important to note that these subclinical changes represent truly harmful outcomes and are not merely homeostatic or physiologic adjustments to the presence of lead.

The toxic effects of lead are evident principally in three organ systems: the erythrocytes and their precursors, the central and peripheral nervous system, and the kidneys. Lead has also been shown to have adverse effects on reproduction in both men and women.[26] It is a potent carcinogen in three animal species.[27]

Hematologic Toxicity

Anemia is the classic clinical manifestation of lead toxicity in the erythrocytes. The severity and prevalence of lead-induced anemia are correlated directly with the blood lead level. The anemia induced by lead may be either normochromic or hypochromic and may be associated with an increased reticulocyte count. It is caused primarily by an impairment of heme biosynthesis, but an increased rate of erythrocyte destruction may also occur. At blood lead levels as low as 10 μg per dl, lead begins to inhibit the cytoplasmic enzyme δ-aminolevulinic acid dehydratase in the heme biosynthetic pathway; the enzyme's inhibition is virtually complete at lead levels of 70 to 90 μg per dl.[28] Also at blood lead levels of 15 μg per dl in children and of 25 to 30 μg per dl in adults, lead begins to inhibit the mitochondrial enzyme ferrochelatase, which is responsible for catalyzing the transfer of iron from ferritin to protoporphyrin to form heme.[29,30] Ferrochelatase inhibition causes the metabolic intermediate erythrocyte protoporphyrin to accumulate to excess in erythrocytes. Erythrocyte protoporphyrin elevation is thus a measure of both lead absorption and toxicity.

Neurologic Toxicity

In the peripheral nervous system, the motor axons are the principal target of lead. Lead-induced pathologic changes in these fibers include segmental demyelination and axonal degeneration.[31] Extensor muscle palsy with wrist and ankle drop has since the time of Hippocrates been recognized as the classic clinical sign of this toxicity.

Recent studies of the peripheral nerves in persons with lead exposure have used electrophysiologic probes to determine whether lead causes covert abnormalities in function. In the first of these studies, evidence of asymptomatic slowing of motor nerve conduction velocity was found in workers whose blood lead levels had never exceeded 70 μg per dl.[32] Most recently, in a prospective study of new entrants to the lead industry, slowing of ulnar nerve conduction velocity was noted at blood lead levels as low as 30 to 40 μg per dl.[33]

In the central nervous system, extensive research has sought to determine whether lead causes asymptomatic impairment in function at doses insufficient to produce clinical encephalopathy. The best-designed studies have been carried out in children. In an early investigation, it was found that clinically asymptomatic children with elevated body lead burdens (as defined by dentine lead levels) had a 4.5-point deficit in mean verbal IQ scores compared with children with lower lead burdens.[34] This finding was still strongly evident after correcting for a

wide range of socioeconomic, behavioral, and biologic factors. Similar results were reported in other early studies.[35-37]

This early work was corroborated by a long-term follow-up of the children in the original study group to age 18.[38] At that time the children who had had higher lead burdens in early life were found to have a higher frequency of reading difficulty, of failure to graduate from high school, and of criminal behavior.[38]

Most recently, evidence for the neuropsychologic toxicity of lead at low doses has been provided by a series of prospective studies of newborn children.[39-41] In each of these investigations, correlations have been sought between intellectual performance in young children and umbilical cord blood lead levels at birth. All of these studies have found subclinical but apparently irreversible decrements in central neurologic function. This dysfunction is characterized by diminished intelligence, shortened attention span, and slowed reaction time. These findings are highly credible. They have been accepted by the Centers for Disease Control and Prevention as the basis for revamping the national strategy for preventing lead poisoning in the United States,[6] and they have been accepted also by the National Academy of Sciences in their recent authoritative review of childhood lead poisoning.[42]

An unexplored implication of the finding that lead causes insidious asymptomatic injury to the central nervous system is that some as-yet-unknown fraction of cases of presenile dementia, motoneuron disease, or other chronic neurologic and psychiatric conditions may possibly be caused by long-term exposure to lead.[43] Such long-term exposure may result in an accelerated attrition of neurons that becomes clinically evident with age. Epidemiologic and clinical studies to assess previous lead exposure in persons with chronic neurologic disease such as Parkinson's disease, motoneuron disease, and dementia will be needed to assess this possibility.

Renal Toxicity

Chronic nephropathy, which may progress to kidney failure, is the classic renal manifestation of lead toxicity. It appears to result from long-term, relatively high-dose exposure to lead.[44] The cells lining the proximal tubules appear to be the tissue in the kidneys most highly sensitive to lead.[29] In these cells, at blood lead levels of 40 to 80 μg per dl, lead induces the formation of dense intranuclear inclusion bodies consisting of a lead-protein complex.[29] Hyperuremic gout, apparently resulting from increased reabsorption of uric acid by the tubular cells, is a metabolic correlate of lead-induced renal impairment.[29]

The evolution of lead nephropathy is usually silent. The central event appears to be the progressive destruction of tubular cells and their replacement by fibrosis.[45] Clinical manifestations of impairment, consisting of elevations in blood urea nitrogen or serum creatinine levels, do not ordinarily become evident until 50% to 75% of the nephrons have been destroyed. The later stage of lead nephropathy is characterized pathologically by interstitial fibrosis with atrophy and dilation of the tubules and relative sparing of the glomeruli; in this stage, intranuclear inclusions are infrequent.[29]

An excess mortality from renal disease has been observed in epidemiologic studies of lead workers.[46-49] In each of these investigations, a twofold to threefold increase has been noted in the number of deaths from chronic nephritis. In one study, an association was observed between the duration of employment in a lead smelter and death from nephritis.[49]

Lead and Hypertension

Long-term, high-dose exposure to lead was reported early in this century to be associated with an increased incidence of hypertension and cerebrovascular accident.[50] With the reduction in lead exposure that has occurred in most industries, these overt associations are now noted less commonly. Several recent epidemiologic studies, however, have found evidence that lead absorption, even at relatively low levels, is associated with a substantial elevation in blood pressure.[51] Toxicologic studies have also documented an association between increased lead absorption and hypertension.[52] These effects appear to be mediated both through the toxic effects of lead on the kidneys and by direct action on vascular smooth muscle.

Reproductive Toxicity of Lead

A body of experimental evidence indicates that lead at high doses is toxic to reproductive function in both male and female laboratory animals.[26] Also, clinical reports, most of them from the first half of this century, described reproductive toxicity in workers of both sexes with high-dose exposure to lead; the incidence of spontaneous abortion was reported to be increased in female lead workers and in the wives of male lead workers.[53]

In male workers with heavy exposure to lead (mean blood lead level, 74.5 μg per dl) and also in men with moderately increased lead absorption (mean blood lead level, 52.8 μg per dl), decreased sperm counts and an increased prevalence of morphologically abnormal sperm have been reported.[54] Two more recent studies also noted sperm count depression at relatively high blood lead levels (>60 μg per dl).[55,56] Studies are needed to assess the possible toxicity of lead to male reproduction at lower levels of exposure and using state-of-the-art biologic markers of sperm function.

Recent Research Developments

A major research need in lead poisoning is a method to assess long-term lead exposure. A newly applied technology that holds promise for the accurate, noninvasive assessment of long-term lead exposure is the measurement of the bone lead concentration by x-ray fluorescence analysis. This technique offers a relatively rapid approach to the individual assessment of body lead burdens.[57,58] It takes advantage of the fact that the half-life of lead in bone is approximately 10,000 days (25 years).[18] Moreover, the radiation dose is minimal, amounting to only about 0.2% of the radiation delivered by dental x-ray studies.

X-ray fluorescence analysis may be undertaken using either K or L x-rays, and instruments of both types have been developed.[59,60] The K instrument has several intrinsic advantages over the L instrument.[61] First, the K instrument samples lead across the entire transverse section of bone, in contrast to the L instrument, which obtains 90% of its signal from only the most superficial 2 mm. If there is variation in the concentration of lead across the bone, the L measurement will fall victim to this variation, but the K will not. In addition, the K instrument does not require a measurement of the thickness of the overlying skin, whereas the L instrument is sensitive to any error in the required measurement of skin thickness. Third, the K instrument is relatively insensitive to movement of the subject during the sampling period, whereas the L instrument is very sensitive to movement; given that the typical sampling time is about 15 minutes, this consideration is not trivial. Finally, the L x-ray fluorescence instrument has not been well validated. In defense of the L instrument, there may be detailed modeling studies in which it will be desirable to examine lead content simultaneously in several bone compartments. In such circumstances, the combined use of the K and L instruments might offer uniquely valuable information on the kinetics of lead.

The future use of x-ray fluorescence analysis in workers and children exposed long term to lead will refine current knowledge of the relationships between cumulative lead exposure and its toxic effects on the nervous system, kidneys, cardiovascular system, and reproductive organs.[62]

Current Issues and Controversies

How Frequently Should Young Children Be Screened for Lead?

The Centers for Disease Control and Prevention and the American Academy of Pediatrics have recommended that all preschool children in the United States be screened for lead.[6] We concur in this recommendation. Although screening for blood lead in children is somewhat costly, the price per test is coming down. Moreover, the analysis can be done on a carefully obtained fingerstick blood specimen; if state-of-the-art instruments are available and a child's finger is scrupulously cleaned, venipuncture is not required. The public health benefits of the early detection of lead intoxication in children are so great that the performance of at least a single blood lead measurement on all American children is well justified.

If only a single blood lead determination is to be done on a child, the most logical time to do it is between the ages of 1 and 2 years. Most studies of the distribution of blood lead levels have shown that the highest levels are seen in 1-, 2-, and 3-year-olds. Moreover, detecting an elevated blood lead level at an early age increases the opportunities for intervention.

If in the judgment of a pediatric practitioner a child is at high risk of lead poisoning, then the child will need to be screened more frequently. The Centers for Disease Control and Prevention has developed a series of indicators of high risk (Figure 1).[6] If a child is found through a brief history to have one or more of these risk factors, testing ought to proceed more frequently, with the exact frequency being determined by the pediatric practitioner, possibly in consultation with the state or local health department. When repeated screening is targeted to those children at highest risk, the direct effects of lead testing programs on other public health programs such as childhood immunization will be minimized.

Prepregnancy Screening for Lead

It has become common practice in obstetrics in the United States to screen women for rubella and hepatitis B antibody status before the conception of a planned pregnancy. It is not standard at the present time to measure the blood or bone lead level in a woman who intends to become pregnant. This is an issue that appears worthy of investigation.

The underlying hypothesis is that lead in the bone may become mobilized during pregnancy and could then cross the placenta to reach the fetus. Now that relatively inexpensive diagnostic methods exist for determining blood and bone lead levels and given that bone lead instruments will likely become widely available in the years ahead, research should be undertaken to assess whether prepregnancy bone lead screening is worthwhile in women who may have had a past exposure to lead. Hypothetically, if the bone lead concentration is found to be elevated, chelation therapy could be prescribed before the pregnancy is conceived to reduce the body lead burden. Chelation therapy is clearly contraindicated during pregnancy because the possibility exists that the chelating agent may enhance the movement of lead across the placenta.

This issue will require further research and assessment

Does your child

- live in or regularly visit a house built before 1960 with peeling or chipping paint? This could include a day-care center, preschool, or the home of a babysitter or a relative.
- live in or regularly visit a house built before 1960 with recent, ongoing, or planned renovation or remodeling?
- have a brother or sister, housemate, or playmate being observed or treated for lead poisoning—that is, blood lead level ≥15 μg per dl?
- live with an adult whose job or hobby involves exposure to lead?
- live near an active lead smelter, battery recycling plant, or other industry likely to release lead?

Figure 1.—The questions in this figure were developed by the Centers for Disease Control and Prevention[6] to assess the risk of high-dose exposure to lead.

in the years ahead. No recommendation except further study is justified at present.

Should Workplace Protection Be More Stringent?

Data developed over the past 10 to 15 years clearly indicate that lead causes toxicity among workers at levels of exposure below the current permissible exposure limit established in 1978 by OSHA.[1,2,16] This exposure limit allows blood lead levels in American workers to be as high as 50 μg per dl. Hypertension and neurologic impairment are documented to occur at blood lead levels below 50 μg per dl, and it is possible that long-term exposure at this level may result in renal impairment.[63]

A most difficult problem in occupational lead exposure is raised by the recently reported finding that lead causes neurologic damage to fetuses at blood lead levels as low as 15 to 20 μg per dl—levels substantially below current workplace exposure standards. This finding has been noted in three separate prospective studies and appears highly credible.[39-41] Lead passes virtually unimpeded across the placenta, and the neurologic impairment that it produces in fetuses appears to be irreversible.

The central problem here is a profound mismatch between current occupational standards for lead and human biology.

We strongly recommend on the grounds of preventing systemic toxicity in workers and toxicity to fetuses that the permissible blood lead level in workers be lowered to 10 μg per dl.[2]

Should X-ray Fluorescence Assessment of Lead in Bone Be Used Routinely in Leadworkers?

At present the only medical screening of leadworkers that is required is periodic determination of the blood lead level. Industrial managers have become skilled at maintaining workers' blood lead levels below permissible exposure limits. This goal has been achieved by a combination of reducing workplace exposures plus rotating workers out of heavily contaminated jobs if and when their blood lead levels begin to approach the permissible exposure limit. The problem with this approach is that although blood lead levels today seldom exceed the biologic limit value, workers continue to be at risk of depositing substantial amounts of lead in bone. Thus, the bone lead level can rise steadily even while the blood lead level is kept within legal limits. This situation may increase the risk of long-term toxicity.

In the future, as x-ray fluorescence instruments become more widely available, it may be necessary to consider incorporating the determination of lead in bone by this method into the standard medical monitoring of leadworkers. Annual or biennial determinations of bone lead content in any leadworker would supplement the periodic determination of blood lead levels. If such a requirement were to be developed, it would need to be linked to the provisions for medical removal protection and rate retention that currently are included in the OSHA occupational lead standard.[14]

How Should the Federal Government Deal With the Problem of Lead Abatement?

Because millions of housing units in this country are contaminated with lead paint, it is clear that the prevention of lead-paint poisoning in current and future generations of American children will require massive abatement of this material. A major need is the development of a large cadre of workers who have been properly trained and certified in lead abatement. Such a cadre exists already for the abatement of asbestos. These workers have been trained under the provisions of the Asbestos Hazard Emergency Response Act. Similar legislation and similar training requirements will be necessary for leadworkers.

An unresolved issue is the source of funding for lead abatement. The cost will be enormous. It is not fair to require that landlords pay these costs in their entirety, since in many cases they were unaware of the lead hazard when the buildings were purchased. Tenants also should not be expected to pay the cost. Governmental bodies will inevitably be required to pick up a portion of the costs and perhaps also to provide tax write-offs for renovations. An innovative proposal has been made to impose a stiff excise tax on new lead as a means of financing lead-paint abatement.[64] The attractiveness of this proposal is that it will penalize the corporations that profited in the past from sales of lead-based paint at a time when the hazards of this paint were already widely known. This proposal deserves serious consideration.

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Epitomes

Important Advances in Clinical Medicine

Obstetrics and Gynecology

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The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in obstetrics and gynecology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Obstetrics and Gynecology of the California Medical Association, and the summaries were prepared under the direction of Dr Chang and the panel.

Group B Streptococcal Infections in Pregnancy

Group B streptococcus (*Streptococcus agalactiae*) is a perinatal pathogen with substantial maternal and neonatal morbidity and mortality. A study by the Centers for Disease Control and Prevention estimated that more than 15,000 cases and more than 1,300 deaths are caused by group B streptococcal infection in the United States each year. The economic effects are also considerable. In 1985, the cost of group B streptococcus infection was estimated to be $726 million for one year. This included obstetric cases ($269.6 million), early-onset neonatal group B streptococcal sepsis ($243.9 million), and late-onset neonatal sepsis ($213.3 million).

Maternal morbidity included cystitis, pyelonephritis, preterm labor, premature rupture of membranes, chorioamnionitis, postpartum endometritis, wound infections, bacteremia, and sepsis.

Neonatal infection with group B streptococcus can be classified as early- or late-onset. The incidence of early-onset infection—occurring in the first week of life—is 1/1,000 to 3/1,000 live births. Most infants are diagnosed within the first 48 hours; two thirds are symptomatic within six hours of birth. The clinical presentation is usually septicemia, pneumonia, or meningitis. Reported mortality ranges from 15% to 55%.

Late-onset neonatal infection occurs after the first week of life, up through 12 weeks of age. The incidence is 0.5/1,000 to 1.0/1,000 live births. Infants usually present with meningitis (80% to 85%), and mortality rates are lower (10% to 20%). Unfortunately, as many as half of infants who have meningitis will have long-term neurologic sequelae—cranial nerve palsies, subdural effusions, seizure disorders, cognitive dysfunction, deafness, and learning disabilities.

Asymptomatic vaginal colonization with group B streptococcus is common in pregnancy, occurring in 4.6% to 40% of women. Variables affecting carriage rates include age, race, parity, geographic location, duration of gestation, location, and number of sites cultured. An increased risk is seen with older age, African-American race, third-trimester gestations, patients living in the Southeast United States, and those patients who have both a vaginal and a rectal swab sent for culture. Vaginal and rectal swabs have the highest yield of positive cultures, and isolation rates from the cervix are the lowest. Laboratory methods are also important: if selective media (Todd-Hewitt broth with added nalidixic acid, gentamycin, and sheep blood) are not used, the false-negative rate may be as high as 50%.

Infection occurs by vertical transmission from mother to fetus. Transmission of group B streptococcus may follow rupture of membranes, may occur in the presence of intact membranes, or may be acquired intrapartum. Infants born to colonized mothers have a 42% to 72% risk of being infected; infants born to noncolonized mothers have an 8% risk of becoming colonized. Although almost two thirds of infants born to colonized mothers become colonized themselves, it is important to recognize that only 1% to 2% become infected at parturition. Nosocomial transmission also occurs and may play a role in late-onset neonatal infection.

The rate of neonatal infection is dramatically increased if a mother is heavily colonized or in the setting of prolonged rupture of membranes or prematurity, amniotic fluid colonization, intrapartum fever, or has a history of another child who was infected.

Efforts to prevent neonatal group B streptococcus infection by maternal antepartum screening and treatment are ineffective. Maternal colonization status is variable, with spontaneous clearing and recolonization, with or without treatment. In addition, antepartum screening cultures are not predictive of colonization status intrapartum. Even if antepartum screening cultures were predictive of intrapartum status, this would result in treating 100 women to prevent one or two neonatal infections, which would be expensive, would involve the risk of anaphylactic reactions, and could select out resistant organisms.

Selective intrapartum antibiotic chemoprophylaxis

has been shown to be effective in reducing the rate of neonatal group B streptococcus infection. The American College of Obstetricians and Gynecologists recommends intrapartum antibiotics in patients with the following risk factors: preterm labor (less than 37 weeks), preterm premature rupture of membranes (less than 37 weeks), prolonged rupture of membranes (more than 18 hours), a previous child infected with group B streptococcus, or maternal fever during labor.

Treatment should consist of ampicillin, 2 grams intravenously every six hours, or penicillin G, 5 million units intravenously every six hours until delivery. Women allergic to penicillin may be treated with clindamycin or erythromycin.

Selective screening cultures may be helpful in populations with an increased incidence of neonatal group B streptococcal infection, in women with arrested preterm labor, with premature rupture of membranes remote from term, and those undergoing surgical procedures of the cervix in pregnancy.

Currently, none of the diagnostic tests available for group B streptococcal infection is rapid enough or has high enough sensitivity and specificity to allow more accurate prophylaxis directed at patients who would benefit most. Maternal vaccines are being developed and may play an important role in prevention of this infection in the future.

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Multiple Marker Screening

OBSTETRICIANS AND GYNECOLOGISTS are always searching for a noninvasive way to screen for genetic abnormalities of the fetus. Of particular interest is Down's syndrome, the most common serious chromosome disorder, occurring in 1 in 800 newly born infants. Most of these are due to nondisjunction (usually in meiosis 1) causing a trisomy 21. Nondisjunctional events occur more frequently with advanced maternal age. Age-specific rates of Down's syndrome are available.

Until 1988, women were offered only amniocentesis or chorionic villus sampling, both invasive procedures involving some risk to the pregnancy. Between 1984 and 1988 several investigators began reporting on serum markers. Maternal serum α-fetoprotein (MSAFP) levels were found to be low in association with fetal aneuploidy, and elevated human chorionic gonadotropin (hCG) levels were found in many Down's syndrome pregnancies, along with reduced maternal serum unconjugated estriols. Several prospective studies have reported the usefulness of varied combinations of these markers in screening for Down's syndrome pregnancies. Although a specific protocol cannot be suggested, at least a double marker or a triple marker offers notably enhanced sensitivity and specificity in the detection of the pregnancy at risk. The value of routine ultrasound studies as a fourth marker has yet to be established.

Screening in women older than 35, to whom prenatal diagnosis of some type traditionally has been offered, appears to have promise. Because the frequency of a positive result is relatively high in this population and because detection is less than with amniocentesis or chorionic villus sampling, it is difficult to recommend replacement of these tests by multiple-marker screening in women older than 35.

Other chromosomal disorders can be detected, to a lesser extent, using multiple markers. In trisomy 18, all three markers are reduced. Trisomy 13 may be detected in some cases as well. Testing for neural tube defects using MSAFP alone may be done simultaneously using standardized cut-off levels.

In California, plans are under way to replace the state MSAFP program with a triple-marker screening program. A start-up date in early 1995 is anticipated. Triple-marker screening will be offered at between 16 and 18 weeks' gestation, with appropriate counseling, to women younger than 35. Women older than 35 will be offered the choice of amniocentesis or chorionic villus sampling or triple-marker screening. If a patient chooses the screen, however, and it indicates a risk less than that of a 35-year-old (using age alone as a criterion), she cannot then choose to have an amniocentesis and must, therefore, be carefully counseled regarding potential false-negative test results.

Ongoing studies are looking at other markers including pregnancy-specific β_1-glycoprotein and leukocyte alkaline phosphatase, which may offer further specificity and a wider range of detection of abnormalities. The future of noninvasive testing looks bright. The vast numbers of women who will be tested in California in the coming years should provide further information about the reliability and cost-effectiveness of mass screening.

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The Acquired Immunodeficiency Syndrome in Women

WOMEN ARE AMONG the fastest-growing groups of persons with the acquired immunodeficiency syndrome

(AIDS) in the United States, accounting for 6,571 cases in 1992, or 13.4% of all reported AIDS cases. Because there is a long lag period between infection with the human immunodeficiency virus (HIV) and the development of AIDS, and because rates of heterosexual transmission are increasing in the United States, most authorities believe women account for an even larger proportion of all persons with HIV infection. Among women with AIDS reported from 1988 through 1991, injection drug use was the most common transmission mode. In 1992, however, AIDS cases in women attributed to heterosexual transmission exceeded cases attributed to injection drug use for the first time. Some regional variation was observed. Among women in the West, Midwest, South, and US territories, heterosexual contact was the predominant means of transmission, while in the Northeast, injection drug use remained the predominant means. In 1992, among women with AIDS whose infection was attributed to heterosexual contact, 57% had a sex partner who was an injection drug user.

Although HIV transmission could theoretically occur whenever an uninfected person is exposed to body fluids from an infected person, studies indicate that most HIV is transmitted through sex, that penile-anal intercourse carries a higher risk than penile-vaginal intercourse, and that penile-vaginal intercourse carries a higher risk than oral-genital sex. Despite this, many cases of oral-genital transmission have been documented, primarily among gay men. Transmission studies among heterosexual women and men indicate that HIV is probably transmitted more efficiently from male to female than from female to male. Among women with AIDS who report sex with women, most also report a history of injection drug use or having had male partners who were injection drug users. A few reports, however, describe cases that may have been transmitted female to female related to oral-genital intercourse.

Factors that must be considered in evaluating and caring for women with HIV infection include routine gynecologic care, pregnancy prevention, or, if a woman is pregnant and plans to have the baby, preventing perinatal transmission of HIV from mother to infant. In 1993, the Centers for Disease Control and Prevention (CDC) revised the AIDS surveillance case definition to include invasive cervical cancer as an AIDS indicator, further underscoring the importance of gynecologic care and other HIV management strategies for these women. Several researchers have observed that the prevalence of cervical dysplasia is higher among women with HIV infection than among uninfected women with similar risk profiles, and reports from some case series suggest that women with HIV infection may have higher-than-expected rates of cervical cancer. Prospective studies are under way. In the interim, a panel of experts convened at CDC in 1993 provisionally recommended that women with HIV infection should have a Pap smear as part of their initial medical evaluation. If the initial Pap smear results are within normal limits, an additional smear should be obtained within the next six months, and if that smear is normal, repeat smears should be obtained annually. If the initial or follow-up smears show inflammation with reactive squamous cellular changes, another Pap smear should be collected within three months. As is the case for any woman with an abnormal Pap smear, women with HIV infection with abnormal smears should be referred for colposcopic examination.

Although not identified as AIDS-indicator diseases, two other gynecologic conditions besides cervical cancer have been recognized as being related to or complicated by HIV infection: vulvovaginal candidiasis that is persistent, frequent, or unresponsive to drug therapy; and pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess. The effect of HIV infection on the clinical course of pelvic inflammatory disease has not been completely elucidated, but in two studies, women with HIV infection with pelvic inflammatory disease were less likely to have a leukocytosis and were more likely to require surgical intervention for tubo-ovarian abscess. Based on this limited information, CDC recommends routine hospital admittance and intravenous antibiotic therapy for women with HIV infection with pelvic inflammatory disease.

Perinatal transmission occurs in 13% to 39% of pregnancies in women who are infected with HIV, and the virus also can be transmitted through breast feeding. Although the factors associated with perinatal HIV transmission are not completely understood, maternal viremia associated with recent seroconversion or a low CD4 count appears to increase the likelihood of transmission. Cesarean section may be associated with a modest reduction in the risk of perinatal transmission, but randomized controlled trials are needed to define the role of operative delivery. Zidovudine appears to be effective in reducing perinatal HIV transmission. In a randomized, controlled trial, infants born to women taking zidovudine (500 mg orally daily) during mid- to late pregnancy combined with intravenous zidovudine intrapartum and six weeks postdelivery to the newborn, showed significantly lower rates of HIV transmission (8%) compared to infants born to women taking a placebo (26%). For mothers, pregnancy does not appear to accelerate the progression of early HIV infection.

In the absence of a vaccine, the most effective HIV prevention strategy available to women is avoiding sex with a partner with HIV infection. Latex condoms are also highly effective for preventing HIV infection when used consistently and correctly, and women at risk for HIV should be encouraged to carry condoms themselves and to talk with their partners about using condoms. Other barrier methods, including antimicrobial agents used with a diaphragm or applied alone, appear promising; their effectiveness in preventing HIV transmission is still unknown, however. When a male condom cannot be used, couples should consider using a female condom. While results of clinical trials have not been published, the female condom has been shown to be an effective barrier to HIV and other sexually transmitted organisms. As is true for men, sexually active women with risk factors for HIV infection or who live in areas with high HIV

prevalence should be offered or advised to seek HIV counseling and testing.

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The New Progestins

IN AN EFFORT TO DECREASE androgenic side effects, combination oral contraceptive pills have undergone a further refinement. New oral contraceptive formulations are available containing one of these 19-nortestosterone progestins: desogestrel, norgestimate, or gestodene. While other progestin preparations are still available, these new ones have less binding affinity to the androgen receptor and decrease androgen-mediated metabolic changes, weight gain, acne, and hirsutism. When compared to other low-dose—not more than 35 µg ethinyl estradiol—combination oral contraceptive pills, these new formulations were comparable in efficacy, the incidence of breakthrough bleeding, and the absence of withdrawal menses. They had less effect on carbohydrate and lipoprotein metabolism than currently used oral contraceptives. No difference was seen in the incidence of thromboembolic events or an increase in blood pressure with the new progestins.

Before their introduction in the United States, these progestins were extensively tested in Europe. Studies reported increased levels of sex hormone-binding globulin with an associated decrease in free testosterone levels after new progestin use. While all combination oral contraceptives have the ability to decrease androgen-mediated side effects, the new progestins offer clinically proved improvement of acne and hirsutism. With respect to carbohydrate metabolism, women using desogestrel- and gestodene-containing oral contraceptives had small increases in the area under the glucose curve, determined during an oral glucose tolerance test. In comparison, norgestimate formulations caused no changes in carbohydrate metabolism. When compared for their effect on lipid metabolism, new progestins increased high-density lipoprotein (HDL) levels and decreased low-density lipoprotein (LDL) levels to a greater extent than most currently used oral contraceptives. Subtle differences, however, exist among the new progestins. Desogestrel preparations produced the largest average increase (12.9%) in HDL levels, while desogestrel and gestodene formulations were associated with the largest average decrease (2.1% to 2.5%) in LDL levels. All three new progestins increased triglyceride levels (range, 14.8% to 38.3%), with norgestimate and gestodene demonstrating the minimal and maximal average increases, respectively.

Desogestrel-containing oral contraceptive pills are available currently as a monophasic preparation (Desogen, Ortho-Cept) for clinical use. Norgestimate-containing oral contraceptive pills are also available as a monophasic (Ortho-Cyclen) and triphasic (Ortho Tri-Cyclen) progestin preparation. Where competing pharmaceutical companies are producing similar products, there may be a distinct difference in the selling price of the medication. Additional formulations (a gestodene-containing and a desogestrel triphasic preparation) are currently being reviewed by the US Food and Drug Administration. The oral contraceptives are packaged in both standard 21- and 28-day regimens. New progestins have a comparable or longer half-life than current progestins, which minimizes the effect of a missed or late pill ingestion. These medications represent a good initial choice for the first-time oral contraception user.

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Laparoscopically-Assisted Hysterectomy

THE USE OF THE LAPAROSCOPE during hysterectomy has generated much interest and controversy. Terms such as "laparoscopically-directed hysterectomy," "laparoscopically-assisted vaginal hysterectomy," and "laparoscopic hysterectomy" are often used interchangeably and represent a spectrum of laparoscopic procedures. Diagnostic laparoscopy before standard vaginal hysterectomy may help surgeons detect unsuspected pelvic pathology. Operative laparoscopy is used to treat conditions that would have prevented a safe vaginal approach ("directed") or to "assist" the hysterectomy by doing some of the dissections, ligations, and incisions laparoscopically that would have otherwise been done vaginally. Total laparoscopic hysterectomy involves the complete laparoscopic ligation of uterine blood supply and supporting ligaments. The surgical steps are the same as for abdominal hysterectomy, but the uterus is usually delivered vaginally.

The laparoscopic approach has potential advantages over standard vaginal hysterectomy. It allows safer and better adnexal surgical procedures when benign ovarian pathology is present, provides better uterine descensus and thus facilitates vaginal surgical procedures, offers better pelvic overview both before and after a surgical procedure, and allows lysis of adhesions and treatment of endometriosis. It can also be used to treat other pelvic conditions. The main advantage of this procedure is its potential ability to convert many abdominal cases into vaginal ones. There has been concern about the potential risks of complications and increased anesthesia and operating time. In expert hands, however, this procedure rarely exceeds two hours, and current series have not reported

higher rates for these operative complications. There have been reports of ureteric injuries, postoperative bleeding, and hematomas with the use of endoscopic staple devices.

The nature of this new technique has ethical, medicolegal, and economic ramifications. Whether the laparoscopic procedure is going to replace a good number of abdominal surgical procedures is uncertain at this time. Early reports have shown that in expert hands the immediate morbidity, mortality, and postoperative course of these procedures are comparable to their vaginal counterparts and better than their abdominal ones. Numbers are still limited, and there are no long-term follow-up studies. An important concern is whether these numbers represent a bias because published reports have mostly come from expert laparoscopists. Retrospective analysis of 50 laparoscopically-assisted vaginal hysterectomy procedures done in a residency setting indicate that perioperative complications occur in 12% of patients, compared to 26% for abdominal hysterectomy and 6% for vaginal hysterectomy. The most common complications were febrile morbidity, abdominal wall ecchymosis, and intraoperative bleeding requiring transfusion, occurring in 4%, 4%, and 6% of patients, respectively. All these complications were managed conservatively. With laparoscopically-assisted vaginal hysterectomy procedures, hospital costs (about $10,000) are comparable to those with abdominal hysterectomy (about $12,000) but notably higher than for vaginal hysterectomy (about $8,000).

Laparoscopically-assisted hysterectomies are technically difficult and developing the necessary skills is typically associated with a slow learning phase. We recommend that procedures be done with the assistance of an experienced surgeon until one feels comfortable without supervision. Appropriate proctoring is important.

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Assisted Reproductive Technology

SUCCESS RATES FOR ASSISTED reproductive technology continue to improve and availability has become widespread. More than 33,000 cycles of treatment are initiated annually, with delivery rates ranging from 15% to 27% per retrieval. Improvements in embryo freezing have further increased overall success. More than 4,800 frozen embryo transfers resulted in an additional 11% delivery rate per transfer.

The growth of assisted reproductive technology has accelerated research efforts in all aspects of reproduction. This relates particularly to bettering the understanding of spermatogenesis, oocyte maturation, fertilization, preembryo growth and development, and implantation. Exciting and innovative developments have occurred with respect to micromanipulation for the treatment of male infertility; the application of oocyte donation to women of advanced reproductive age; and the reexamination of the unstimulated cycle and its value to in vitro fertilization.

In men, 40% of infertility results from abnormalities in gamete production. In vitro fertilization success rates have been low in these couples compared to patients with tubal disease. An inability to fertilize oocytes represents the greatest problem these men encounter. Pregnancies and births following micromanipulation have been reported in men previously unable to fertilize, using procedures such as partial zonal dissection, subzonal insemination, and most recently intracytoplasmic sperm injection. In experienced hands, pregnancy rates as high as 30% per embryo transfer and, more impressively, 22% of retrieval cycles have been reported following the application of intracytoplasmic sperm injection.

Oocyte donation to women of advanced reproductive age (older than 40 years) has opened up therapy to a new subset of patients. Success measured by implantation rates, clinical pregnancy rates, and, most important, delivery rates in recipients between the ages of 40 and 60 years have been no different from that of their younger counterparts. Presently more than 1,000 oocyte donation cycles are done annually. The method involves synchronizing young, fertile oocyte donors undergoing controlled ovarian hyperstimulation and transvaginal ultrasound-directed follicle aspiration and hormonally prepared functionally agonadal recipients. Delivery rates are typically reported between 25% and 40% per embryo transfer. Guidelines published by the American Fertility Society should aid the practitioner in selecting appropriate candidates for treatment.

Combining assisted reproductive technology and a patient's own natural cycle has reemerged. Pregnancy rates per retrieval are highest when using controlled ovarian hyperstimulation. There are disadvantages related to the high cost of medications, the need for expensive surveillance methods, and the multiple birth rate that follows the transfer of supernumerary embryos, however. Unstimulated cycles take less time, are less traumatic, are less expensive, and result in singleton pregnancies. Pregnancy rates per retrieval are lower using unstimulated in vitro fertilization (28% versus 14%); the embryo implantation rates are actually higher (13% versus 9%), however. Accordingly, life-table analysis indicates that two to three cycles of unstimulated in vitro fertilization yield the same likelihood of pregnancy as a single cycle of controlled ovarian hyperstimulation. Given the reduced cost of the unstimulated approach, repetitive attempts on an individual basis become reasonably cost-effective.

As illustrated by the above examples, assisted reproductive technology now includes multiple measures to treat patients once considered hopelessly infertile. Successful resolution of a patient's infertility warrants careful attention to the treatment plan and the appropriate selection of various approaches.

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Alerts, Notices, and Case Reports

Rapidly Fatal Hyperammonemic Coma in Adults

Urea Cycle Enzyme Deficiency

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DEFICIENCIES OF FOUR urea cycle enzymes—ornithine transcarbamylase (OTC), carbamoyl-phosphate synthetase, argininosuccinate synthetase, and argininosuccinase—are most commonly diagnosed in the neonatal or early childhood years with the onset of hyperammonemia, lethargy, and vomiting.[1] Cases of late-onset urea cycle deficiencies, defined as those that have clinical onset after age 28 days,[2] have been reported less commonly. Ornithine-transcarbamylase deficiency, the most frequently occurring urea cycle enzyme deficiency, is an X-linked inborn defect. This deficiency, usually diagnosed in male neonates, often results in death before 1 year of age. In females, a random inactivation of X chromosomes in hepatocytes leads to a wide spectrum of hepatic OTC activity. Thus, females with partial OTC deficiency may display a wide variety of clinical symptoms. Affected persons may be virtually asymptomatic, or fatal hyperammonemic coma may develop.[1,3-6] The other urea cycle enzyme deficiencies are inherited in an autosomal recessive manner and can be identified only by enzyme assays. These deficiencies also have late-onset phenotypes. In general, the late-onset group of urea cycle enzyme deficiencies is characterized by variability of clinical expression and episodically occurring hyperammonemia and symptoms. This clinical variability makes early diagnosis difficult, which can lead to fatal outcomes. We report a case of previously undiagnosed OTC deficiency in a man who died in a hyperammonemic coma.

Report of a Case

The patient, a 38-year-old man, presented to the University of Nevada Medical Center (Las Vegas) emergency department with symptoms of blurred vision and intermittent blindness. According to his wife, he had been in good health until two weeks before admission when nausea with intermittent vomiting and low-grade fevers developed. His physician had treated him with antibiotics, omeprazole, and dicyclomine hydrochloride, but his symptoms persisted. The morning of admission, the patient was confused and had visual disturbances.

The patient had no major past medical problems. He had been taking fluoxetine hydrochloride for mild clinical depression. He smoked a pack of cigarettes daily but consumed no ethanol and did not use any recreational drugs. His medications the day of admission included fluoxetine, clarithromycin, and omeprazole. He worked as a waiter and was a vegetarian.

On examination, the patient was agitated and had a temperature of 37.2°C (99°F), a regular pulse rate of 78 beats per minute, a blood pressure of 125/77 mm of mercury, and was in no apparent distress. His skin was warm and dry without lesions. His head and neck were normal, and there were no meningeal signs. His heart and lungs were normal. He was confused and could not follow simple commands; however, he responded to verbal, tactile, and painful stimuli. Deep tendon reflexes were symmetric.

Laboratory values included a leukocyte count of 11.4 $\times 10^9$ cells per liter (11,400 per mm^3), hematocrit 0.55 (55%), normal electrolytes, serum creatinine level 80 μmol per liter (normal, 44 to 106 [0.9 mg per dl]), blood urea nitrogen 8.2 mmol per liter (normal, 2.1 to 7.1 [23 mg per dl]), and serum glucose 6.9 mmol per liter (normal, 3.9 to 6.1 [124 mg per dl]). Serum calcium, phosphorus, magnesium, and albumin values were within normal ranges. The serum aspartate aminotransferase level was 39 U per liter (normal, 5 to 35), the serum alanine aminotransferase was 64 U per liter (normal, 7 to 56), total bilirubin 22 μmol per liter (normal, 0 to 20 [1.3 mg per dl]), and prothrombin time 13 seconds (normal, 11 to 13). Arterial blood gas measurements with the patient breathing room air revealed a pH of 7.44, P_{CO_2} 37 mm of mercury, and P_{O_2} 89 mm of mercury. A computed tomographic (CT) scan of the head was normal, and the cerebrospinal fluid revealed no cells and had a protein content of 0.1 gram per liter (normal, 0.12 to 0.6 [10 mg per dl]) and a glucose concentration of 4.8 mmol per liter (86 mg per dl). Cerebrospinal fluid VDRL test was negative.

After admission to a medical ward, the patient became progressively stuporous and then comatose over the next several hours. He was then intubated for airway protection. After he became comatose, tonic-clonic seizure activity developed. An electroencephalogram (EEG) confirmed status epilepticus. He was treated with phenytoin and phenobarbital, but still had continuous seizure activity. Because of minor abnormalities in hepatic function, a plasma ammonia level was measured and was 320 μmol per liter (normal, 18 to 54 [545 μg per dl]) on the second hospital day. A second EEG suggested a diffuse encephalopathic process and generalized seizure activity. The head CT scan was repeated and showed diffuse cerebral edema and early uncal herniation. On the third hospital day, he was pronounced "brain dead." His plasma

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
EEG = electroencephalogram
OTC = ornithine transcarbamylase

ammonia level was 1,021 μmol per liter (1,739 μg per dl).

Liver tissue was obtained within an hour of death and immediately frozen at −70°C. Postmortem liver examination revealed an ornithine-transcarbamylase activity of 184 μmol per hour per gram of tissue in the liver (normal, 1,500 to 9,000). There was normal carbamoyl-phosphate synthetase activity.*

A family history revealed no similar symptoms in the patient's male relatives. He had no offspring.

Discussion

The enzyme OTC is the product of an X-linked gene. Thus, male neonates with an abnormality at this locus are most severely affected. In contrast, female heterozygotes either may have no symptoms or, conversely, fatal sporadic hyperammonemic episodes may develop, especially in times of physiologic stress such as childbirth.[3-5] This variability is due to random inactivation of X chromosomes in hepatocytes, leading to a spectrum of OTC activity. To date, there have been several reports of patients with late-onset OTC deficiency, most of whom are female patients. Cases of symptomatic OTC deficiency have been reported in men as old as 58 years.[6-8] Symptoms at presentation in these male patients with late onset of symptoms vary, but vomiting and lethargy are most common. Those patients whose symptoms occur late are more likely to die at presentation, often of delays in diagnosis.[2] Ultimately, death can result from increased intracranial pressure, the major physiologic response to hyperammonemia. This cerebral edema may be a direct consequence of astrocytes swelling because other brain cells are not affected. Because of astrocytes' close relationship with cerebral blood vessels, it is possible that astrocyte dysfunction leads to the abnormalities in cerebral blood flow seen in animal models of hyperammonemia.[1]

In general, the early symptoms of urea cycle enzyme deficiencies are intermittent and nonspecific, whereas the acute signs of hyperammonemia are vomiting, lethargy, and coma (Table 1). Our patient displayed many clinical clues that retrospectively suggested the presence of an inborn error of ureagenesis. He was a vegetarian, which is a self-selected avoidance of protein. In the acute stage, he had the most common presenting symptoms of OTC deficiency, vomiting and lethargy. He also had intermittent blindness, which has been documented with late-onset OTC deficiency and may be due to early cerebral edema and partial uncal herniation.[9,10] Other symptoms can resemble those found in focal neurologic defects seen with ischemic cerebrovascular disease,[11] intermittent episodes of confusion, migraine headaches, seizures, bizarre behavior, or psychomotor delay.[12] The treatment of seizures in these patients may exacerbate hyperammonemia.[13] A very low blood urea nitrogen level on initial laboratory studies may also indicate a defect in ureagenesis.[1] In most cases, hyperammonemia presents without evidence of substantial hepatic dysfunction.[1,3,8]

Previously undiagnosed defects in ureagenesis may present at times of physiologic stress. Hyperammonemic coma of adults has been reported in postpartum women,[3,14] during infectious illnesses, and perioperatively.[1] During such periods of physiologic stress, increased catabolism produces extreme elevations in plasma ammonia levels due to ineffective hepatic metabolism (Table 2).

The diagnosis of a urea cycle enzyme defect in an adult can be definitively made only by measuring enzyme levels in hepatic tissue. Unexplained neurologic symptoms should be evaluated with a plasma ammonia level. If hyperammonemia is present in a patient with metabolic alkalosis without significant hepatic disease, OTC deficiency or another urea cycle enzyme defect should be strongly suspected (Table 3). Plasma citrulline levels are low in patients with OTC deficiency. Measuring urinary amino acid and orotate levels will help to distinguish the type of urea cycle enzyme deficiency; OTC deficiency, the most com-

*Biochemical Genetics Laboratory of the Baylor College of Medicine, Houston, Texas, performed the enzyme activity measurements on the liver tissue.

TABLE 1.—*Clues to the Diagnosis of Urea Cycle Enzyme Deficiencies in Adults*

Episodic lethargy or confusion	Family history
Episodic nausea and vomiting	Low blood urea nitrogen level
Bizarre behavior	Hyperammonemia (with normal or mildly impaired hepatic function)
Seizures	Cerebral edema
Intermittent blindness	Metabolic alkalosis
Protein avoidance	
Unusual headaches	

TABLE 2.—*Factors That May Precipitate Severe Hyperammonemia in a Patient With Deficiency in a Urea Cycle Enzyme*

Postpartum state	Perioperative state
Protein ingestion	Anticonvulsant medications
Infectious disease	

TABLE 3.—*Laboratory Studies in a Patient With Ornithine-Transcarbamylase Deficiency*

Test	*Result*
Plasma acid/base	Metabolic alkalosis
Plasma ammonia	Mildly to severely elevated
Blood urea nitrogen	Very low to normal
Hepatic function tests	Normal or mild abnormalities
Plasma amino acids	Normal*
Plasma citrulline	Low
Urinary amino acids	Normal†
Urinary orotate	Elevated

*Plasma lysine level is elevated in Reye's syndrome.
†Urinary lysine content is increased in lysinuric protein intolerance.

mon deficiency, often presents with high urinary orotate levels. Physicians must also consider Reye's syndrome, lysinuric protein intolerance, and organic acidemias in the differential diagnosis.[1] Plasma lysine levels will generally be elevated with high levels of hepatic aminotransferases in Reye's syndrome. Offspring and family members of patients with a known defect of ureagenesis should be tested for a similar deficiency historically, by measuring plasma ammonia, plasma and urinary amino acid levels, or by genetic analysis in a fetus.[1,15-17]

Specific treatment protocols have been established for neonates with urea cycle enzyme defects and intercurrent hyperammonemia.[1,18,19] The cornerstone of this therapy is the infusion of benzoate and phenylacetate to activate latent biochemical pathways for waste nitrogen disposal as hippurate and phenylacetylglutamine. Hemodialysis can be used for hyperammonemia not responsive to drug therapy. Restricting nitrogen in the diet is essential. Even with the early recognition of a neonatal defect of ureagenesis, impairment in physical and intellectual development and death often occur.[12,20] Treatment in an adult patient with an unknown defect in ureagenesis requires the physician to be aware of this possibility in the differential diagnosis of any acute focal or generalized neurologic impairment. Especially important is a prompt recognition of hyperammonemia in a comatose patient without other signs of hepatic dysfunction. In these patients, an infusion of benzoate and phenylacetate is administered to promote waste nitrogen production, and hemodialysis is indicated when hyperammonemia continues.[1]

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Syphilitic Uveitis

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SYPHILIS REMAINS an uncommon but important cause of uveitis. Syphilitic uveitis is easily mistaken for idiopathic uveitis, particularly in the absence of the characteristic rash of secondary syphilis. A clue to the diagnosis may be the failure of uveitis to respond to corticosteroid treatment.[1] Uveitis may accompany acute syphilitic meningitis, but more often it is a manifestation of secondary or latent syphilis. Although penicillin G benzathine is the usual therapy for secondary or latent syphilis, penetration into the vitreous is poor.[2] Thus, the same concerns regarding the efficacy of penicillin G benzathine in neurosyphilis should apply when treating syphilitic uveitis.

We report the case of a patient with secondary syphilis and moderately severe anterior uveitis. Treatment was based on the anatomy of the eye. We also discuss the pharmacokinetics of penicillin.

Report of a Case

The patient, a 30-year-old man, had a transient flulike illness characterized by chills, anorexia, and an intermittently pruritic rash in March 1992. One to two months later, photophobia, blurred vision, ocular pain, and erythema developed in the left eye. His symptoms lessened slightly over the next six weeks with a regimen of topical cycloplegics and corticosteroids, but they failed to resolve completely. Additional corticosteroids were administered by injection into the episcleral (Tenon's) space with no response. A rapid plasma reagin (RPR) test done two months after his initial presentation to the ophthalmologist was positive at 1:256, with confirmatory antitreponemal immunoglobulin (Ig) M and IgG antibodies detected by enzyme-linked immunosorbent assay (ELISA, Diagnostic Chemicals Limited, Oxford, Connecticut). He said he was not homosexual and did not abuse drugs, and he reported that his last sexual contact was 12 to 15 months before the examination.

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The views expressed herein are those of the authors and do not purport to reflect the position of the Department of the Navy or the Department of Defense.

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ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
ELISA = enzyme-linked immunosorbent assay
HIV = human immunodeficiency virus
Ig = immunoglobulin
RPR = rapid plasma reagin

Physical examination at the time of the positive RPR revealed a hyperpigmented macular rash on his palms, soles, face, back, chest, arms, and legs. No mucous patches, penile ulcers or chancres, or condylomata lata were visible. Adenopathy was prominent in the neck, groin, and epitrochlear areas. He had patchy alopecia of the vertex of the scalp. On ocular examination he had 20/20 vision in both eyes, no afferent pupillary defect, prominent keratic precipitates of the left eye, and cells and flare in the anterior chambers, with 2+ reaction in the left eye and a trace in the right eye.

His chest x-ray film was normal. Tests for hepatitis B and C were negative, as was an ELISA test for antibodies to the human immunodeficiency virus (HIV). The leukocyte count was 6.2×10^9 per liter (6,200 per mm^3) with 0.23 (23%) lymphocytes and 0.09 (9%) monocytes. The erythrocyte sedimentation rate was 49 mm per hour. He had an aspartate aminotransferase level of 38 U per liter with an alkaline phosphatase level of 152 U per liter (normal, <35 and <126, respectively). A lumbar puncture revealed a leukocyte count of 18×10^6 per liter (18 per mm^3) with 0.85 (85%) lymphocytes, a protein content of 0.54 grams per liter (54 mg per dl), and a glucose concentration of 3.2 mmol per liter (58 mg per dl) (63% of the serum value). The cerebrospinal fluid (CSF) VDRL was positive at 1:2.

He was treated with aqueous crystalline penicillin G for ten days, 3 million units administered intravenously every four hours, followed by three weekly doses of 2.4 million units of penicillin G benzathine given intramuscularly. The dosage of prednisone eyedrops was gradually tapered over two weeks. He did not have the Jarisch-Herxheimer reaction nor did his vision worsen during therapy. A slit-lamp examination showed a completely normal appearance after four days of intravenous penicillin therapy. No recurrence of uveitis or additional manifestations of secondary syphilis have been seen after 12 months of follow-up. The CSF abnormalities have returned to normal, and he remains HIV-negative.

Discussion

In 1931 Moore reported that 4.6% of patients with early secondary syphilis had uveitis; in patients with recurrent secondary syphilis, the incidence was 9.3%.[3] In another study, it was estimated that 1.1% of uveitis cases seen in an office practice from 1970 to 1980 were caused by syphilis.[4] More recently, uveitis was reported to be the most common ocular manifestation of syphilis, occurring in 25 of 1,020 new patients (2.45%) seen at a university eye clinic over a five-year period.[5] An association appears to exist between ocular syphilis and neurosyphilis, which may be more pronounced in patients infected with HIV. Of 12 HIV-positive patients with luetic uveitis, all had abnormal findings on lumbar punctures, whereas only two of five HIV-seronegative patients with luetic uveitis had abnormal spinal taps; the ocular disease was more severe in the HIV-positive group.[6]

Patients with persistent uveitis, particularly in the presence of corticosteroid therapy, should be screened for sarcoidosis, toxoplasmosis, tuberculosis, leptospirosis, connective tissue diseases, *Toxocara canis,* and syphilis.[7,8] A rash in association with uveitis suggests syphilis, sarcoidosis, Lyme disease borreliosis, or varicella zoster.[9] The uveitis associated with syphilis frequently worsens with corticosteroid therapy, and this may provide an important clue to the diagnosis.[1] A spontaneous resolution of syphilitic uveitis or a favorable response to corticosteroid therapy may occur, however, and can falsely suggest that the ocular disease is noninfectious.[10,11] Excluding syphilis as a cause of uveitis requires both a nontreponemal and a treponemal test, as the RPR or VDRL alone can be nonreactive in 30% to 75% of cases of syphilitic uveitis.[4,5] In these cases the diagnosis is strongly suggested by a compatible clinical picture with positive treponemal serologic tests (fluorescent treponemal antibody absorption test, microhemagglutination-*Treponema pallidum,* or ELISA), or a vitreous aspirate demonstrating the presence of spirochetes on dark-field or fluorescent microscopy, or both.

The most current published recommendations for the treatment of early syphilis—primary, secondary, or early latent—are to give 2.4 million units of penicillin G benzathine once intramuscularly, regardless of the patient's HIV status.[12] This dose maintains a blood concentration above that minimally acceptable for treponemicide—0.031 IU per ml, or 0.018 μg per ml—for two to three weeks.[13] This regimen is effective but not uniformly curative, however. A review of three studies done in the pre-HIV era in which primary and secondary syphilis was treated with 2.4 million units of penicillin G benzathine found a cumulative retreatment rate of 0% to 7.5%; retreatment represented treatment failures plus all instances of reinfection.[14] A more recent study presents data to show that a single dose of 2.4 million units of penicillin G benzathine is inadequate to cure early syphilis in HIV-infected patients once the central nervous system has been invaded.[15] Patients who did not have HIV infection appeared to be cured.

The eyes may be viewed as an extension of the central nervous system. The central nervous system is involved in as much as 30% of patients with syphilis, and spirochetes have been isolated from the spinal fluid of patients with no other demonstrable CSF abnormalities.[15] Penicillins, including penicillin G benzathine, do not readily achieve adequate concentrations in the anterior chamber of the eye or the central nervous system, due in part to their lipid insolubility and because penicillins are weak acids.[2,16]

The eyes possess two major barriers to drug transport from the systemic circulation into their interior.[2] The retinal capillaries, like those of the central nervous system and the prostate, are nonfenestrated, limiting the passage

of lipid-insoluble drugs into the vitreous humor from the systemic circulation. The retinal pigment epithelium, lying between the retinal capillaries and the choroid, possesses "tight" intercellular junctions that limit lipid-insoluble agents from crossing the cell membranes. These two barriers remain unaffected by inflammatory states such as uveitis. Thus, when a poorly lipid-soluble agent is administered systemically, subtherapeutic drug concentrations in the vitreous are likely to result. The penetration of various penicillins into rabbit vitreous chambers ranges from less than 1% to 10% of the peak serum concentrations.[2]

β-Lactam drugs are eliminated by the "posterior" (or retinal) route through active transport by a retinal pump, which shares many features with the renal tubular cell pump and the choroid plexus of the brain.[2] The vitreal half-life of drugs cleared by the retinal route is often brief because of the broad surface area of the retina, the short distances the drug must travel to the retina from the vitreous, and the active nature of the pump. Retinal route transportation shows saturation kinetics, however, and competitive inhibition by probenecid or other β-lactams can prolong the vitreal half-life of penicillin G.[2]

Treponema pallidum may persist in the body after treatment, particularly in the central nervous system and ocular humors, where treponemicidal concentrations of penicillin are not readily achieved.[2,16] Of note is that some of the previous work on the presence of treponemes in the aqueous humor was confused by artifact.[17] Nevertheless, some studies have used careful methods to minimize artifact and cross-reactivity with nonpathogenic treponemes and other pathogenic spirochetes.[10,18-20] In this way, treponemes with a structure and motility characteristic of *T pallidum* have been repeatedly identified in the aqueous humor of diseased eyes. Animal infectivity tests, however, thought by some to be the gold standard for demonstrating viable *T pallidum* in tissues,[15,21] were done in only a few cases.[19] This sequestration of treponemes likely has therapeutic implications.

Although patients with secondary syphilis frequently have demonstrable CSF abnormalities,[12,15] routine lumbar puncture is not recommended unless clinical neurologic involvement (ophthalmic or otic symptoms, cranial nerve palsies) exists.[12] More than 40 years of experience have shown that parenteral penicillin is effective for the local cure of early syphilis and in preventing its late sequelae, but the optimal dose, duration, and preparation are unknown. Penicillin G benzathine, 2.4 million units given intramuscularly in a single dose, is the current standard recommendation. Some have urged the use of higher doses of penicillin in treating early syphilis.[22]

A patient with secondary syphilis and moderately severe uveitis may be better served with a regimen that provides higher concentrations of penicillin in the vitreous than does penicillin G benzathine, analogous to a patient with neurosyphilis. Before the HIV epidemic, the Centers for Disease Control's recommended treatment of syphilis—including neurosyphilis—of more than a year's duration was three consecutive weekly doses of penicillin G benzathine.[23] Experience in the decades before this recommendation using approximately 4.8 to 6.0 million units of repository penicillin for the treatment of neurosyphilis documented a failure rate of about 10% within two years.[24] The most current guidelines for treating neurosyphilis suggest intravenous aqueous crystalline penicillin G as the recommended regimen, with penicillin procaine (plus probenecid) given intramuscularly as an alternative regimen.[12] Based on pharmacokinetic data, we prefer to use intravenous aqueous crystalline penicillin G for the treatment of patients with syphilitic eye disease.

It has been reported that seven separate reviews of the ocular manifestations of the acquired immunodeficiency syndrome did not note syphilis among the 235 patients described.[11] It would be important not to overlook this possibly treatable cause of visual impairment in HIV-positive patients. The incidence of syphilis is increasing in the United States,[25] and as such, syphilitic uveitis will be seen more often; it may be the feature that brings patients to medical care, as in our patient. The diagnosis should be suspected when uveitis worsens or fails to respond to corticosteroid treatment. The diagnosis can be confirmed by a positive serologic test, a demonstration of intraocular treponemes, or both. Because of anatomic and pharmacokinetic concerns, penicillin G benzathine may be inadequate therapy. It is recommended that syphilitic uveitis be treated with the same penicillin regimens recommended for neurosyphilis.[12]

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Recurrent Pneumonia in Relapsing Polychondritis

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RELAPSING POLYCHONDRITIS is a systemic disease characterized by recurrent inflammatory lesions of cartilaginous structures throughout the body. Inflammation typically involves the external ear, nose, eyes, larynx, trachea, ribs, and joints.[1-3] Respiratory tract involvement is common. Secondary infections of both upper and lower parts of the respiratory system can occur. It is unusual for pneumonia to be the presenting symptom, but in the case we describe, recurrent unexplained pneumonia was the key to the diagnosis.

Report of a Case

The patient, a 38-year-old man, was admitted to R. E. Thomason General Hospital, El Paso, Texas, because for three days he had had cough, pleuritic chest pain, dyspnea on exertion, subjective fever, chills, and a discharge from the left ear. He admitted to hoarseness of his voice for several years and mild knee pain without swelling, especially after walking long distances. There was no history of redness, pain, or swelling of his ears or nasal septum nor any dryness of his eyes or mouth. His medical history was notable for insulin-dependent diabetes mellitus and five previous admissions in the past two years for community-acquired pneumonia (Table 1).

On admission the patient's blood pressure was 100/67 mm of mercury, pulse rate was 112 beats per minute, temperature was 36.8°C (98.2°F), and the respiratory rate was 20 per minute. His left ear showed a purulent discharge. There was no laryngotracheal swelling or tenderness present. Bronchial breath sounds were audible in the right mid-lung field. A 2/6 decrescendo diastolic murmur was heard in the aortic area. There was no evidence of joint tenderness or swelling.

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Laboratory tests showed a leukocyte count of 11.2×10^9 cells per liter (11,200 per mm^3) with 0.75 (75%) segmented forms and 0.19 (19%) bands, a hemoglobin level of 149 grams per liter (14.9 grams per dl), and a hematocrit of 0.442 (44.2%). The serum glucose level was 30.6 mmol per liter (552 mg per dl), with serum ketones present in 1:8 dilutions. A urinalysis was normal. A chest roentgenogram showed an infiltrate in the left upper and lower lobes and right middle lobe. Gram's stain of the sputum showed mixed bacteria, and cultures of specimens from tracheal aspirate and broncheoalveolar lavage did not grow any bacteria. Gram's stain of a specimen of the ear discharge showed gram-positive cocci in pairs; culture grew *Streptococcus pneumoniae*. He was treated with a regimen of intravenous fluids, insulin, and cefuroxime.

The finding that the patient had several episodes of pneumonia prompted a further workup. Bronchoscopy showed laryngeal and perilaryngeal edema, inflamed vocal cords, thin translucent tracheobronchial mucosa, and pronounced tracheobronchial collapse on coughing. A bronchial biopsy specimen showed chronic inflammation. On computed tomographic scan of the thorax, he had a minimal infiltrate in the right middle lobe, without any evidence of tracheal stenosis or collapse. Echocardiogram showed a large aortic root with aortic root sclerosis and mild aortic and mitral regurgitation. On ophthalmologic evaluation there was an old uveitis. An erythrocyte sedimentation rate was 100 mm per hour. A test for anti-SS-A (Ro) antibody was positive. Tests for antinuclear antibody, anti-SS-B (La) antibody, rheumatoid factor, the human immunodeficiency virus, HLA-B27, and a VDRL test were negative. The results of complement studies—CH50, C3, and C4—quantitative immunoglobulins, and serum protein electrophoresis were normal. Sinus series and a roentgenogram of sacroiliac joints and the lumbosacral area were normal. Pulmonary function tests showed a mild restrictive pattern.

A diagnosis of relapsing polychondritis was made on the basis of the tracheobronchial thinning and collapse during bronchoscopy and by the presence of otitis media, uveitis, and aortic root dilatation. Steroid therapy was offered and discussed with the patient, but he declined.

Discussion

Relapsing polychondritis is a rare disease of unknown cause. An autoimmune pathogenesis has been supported

TABLE 1.—*Repeated Hospital Admissions for Pneumonia*

Date	Location of Infiltrate on Roentgenogram	Organism Identified in Sputum Specimen
4/8/91	Right peribronchus	Specimen not collected
10/15/91	Both lungs, patchy	*Staphylococcus aureus*
12/13/91	Left lower lobe	*Haemophilus influenzae*, biotype 2
2/10/92	Left lower lobe	*H influenzae*, biotype 3
12/4/92	Left basilar and right cardiophrenic angle	*S aureus*
2/21/93	Left upper and lower lobes and right middle lobe	None in sputum, but *Streptococcus pneumoniae* in middle ear

TABLE 2.—*Presenting Symptoms or Signs in 159 Patients With Relapsing Polychondritis**

Signs or Symptoms	*Patients, No.*	*Percentage*
Auricular chondritis	35	26
Arthritis	32	23
Ocular inflammation	19	14
Respiratory tract involvement	19	14
Nasal chondritis	18	13
Audiovestibular damage	8	6
Miscellaneous	6	4

*Adapted from McAdam et al.[6]

by the presence of antibodies to type II collagen in two thirds of patients.[4] The syndrome was first described in 1923 by Jaksch-Wartenhorst.[5] The diagnosis of relapsing polychondritis can be made on clinical grounds when at least three of the following six features are present[6]: bilateral auricular chondritis; nonerosive, seronegative, inflammatory polyarthritis; nasal chondritis; ocular inflammation; respiratory tract chondritis; and audiovestibular damage. Common clinical features of relapsing polychondritis are shown in Table 2.

Respiratory tract involvement occurs in as much as 50% of patients as a result of compromise of the cartilage of the laryngotracheobronchial tree and is the leading cause of death.[6] Lower airway disease may be asymptomatic and may be found only on tomography and pulmonary function testing.[7] All reported cases of subglottic strictures[7] and tracheal stenosis[2] were symptomatic. The most common symptoms in relapsing polychondritis indicating airway involvement are breathlessness, hoarseness, cough, stridor, wheezes, and tenderness over the laryngotracheal tree; these tend to occur later in the illness and are harbingers of increasing morbidity.[8]

Many associated diseases have been described among patients with relapsing polychondritis.[1,3,6] Our patient had insulin-dependent diabetes mellitus and a positive SS-A test without xerostomia or xerophthalmia. There are no specific laboratory abnormalities diagnostic of relapsing polychondritis. An increased sedimentation rate, anemia, and leukocytosis have been consistently reported during active disease. The evaluation of respiratory tract symptoms should include conventional radiography, computed tomography, pulmonary function tests including flow-volume curves, and bronchoscopy.[8] The mainstays of treatment include the administration of parenteral steroids, nonsteroidal anti-inflammatory agents, and cytotoxic drugs and the surgical treatment of complications.

Airway involvement in relapsing polychondritis can occur with or without minimal ear and nasal involvement.[9] Chest physicians should be aware of the possibility of relapsing polychondritis in patients presenting with recurrent pneumonia; this syndrome has not been described previously. We considered the diagnosis of middle lobe syndrome, immunoglobulin deficiency, and recurrent aspiration until the diagnosis of relapsing polychondritis was made.

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Topics in Primary Care Medicine

Evaluating Coronary Artery Disease Noninvasively—Which Test for Whom?

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The generally accepted indications for stress testing in patients with coronary artery disease include confirming the diagnosis of angina, determining the limitation of activity caused by angina, assessing prognosis in patients with known coronary artery disease, assessing perioperative risk, and evaluating responses to therapy. In patients with a clinical scenario strongly suggestive of angina, testing is not necessary to diagnose coronary artery disease. The exercise treadmill-electrocardiogram test is the oldest and most extensively used stress test and can be reliably performed in patients who are clinically stable and who have an interpretable resting electrocardiogram. The addition of myocardial imaging agents such as thallium 201, technetium Tc 99m sestamibi, and technetium Tc 99m teboroxime increases the sensitivity and specificity for detecting coronary disease. Pharmacologic agents such as dipyridamole, adenosine, and dobutamine may be used in patients who cannot exercise adequately. Myocardial ischemia can also be evaluated by echocardiography, computed tomography, or magnetic resonance imaging, especially when additional information such as left ventricular and valvular function is desired. We review the indications for the noninvasive evaluation of coronary artery disease and the rationale for selecting a diagnostic test.

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Since the introduction of exercise testing in the 1920s, the noninvasive evaluation of coronary artery disease (CAD) has continued to evolve. In this review we will discuss the place of exercise and pharmacologic stress testing in evaluating possible CAD, with an emphasis on appropriate patient and test selection.

Indications for Noninvasive Evaluation

The generally accepted indications for exercise testing include confirming a diagnosis of angina, determining the limitation of activity due to angina, assessing prognosis in patients with known CAD, assessing perioperative risk, and evaluating responses to therapy. In patients with clinical signs and symptoms strongly suggestive of angina, stress testing is not necessary to diagnose CAD. In patients in whom the presence of coronary disease is less clear, especially in those whose symptoms are atypical, clinical suspicion can be colored by the presence of known coronary risk factors—elevated low-density-lipoprotein or low high-density-lipoprotein cholesterol levels, smoking, hypertension, family history, diabetes mellitus—or an abnormal electrocardiogram (ECG) or chest roentgenogram. When pretest probability is high, the physician should consider doing noninvasive testing to provide another "risk factor" in estimating the patient's proclivity for disease. This testing will also give the clinician a sense of the severity of disease. In a patient with known stable angina, noninvasive testing provides information about outcome and response to antianginal therapy and also identifies patients who may benefit from revascularization. In general, stress testing should be considered in patients with stable angina before catheterization if invasive treatment is being considered (Table 1).

Screening asymptomatic patients is an area of considerable interest because silent CAD is an important cause of premature death; many of these patients have three-vessel CAD or left main coronary artery stenosis.[1] Little is known, however, about the effects of intervention on asymptomatic disease, and screening strategies for asymptomatic coronary artery disease have been difficult to justify. Of patients with a low pretest probability of CAD, only about 20% with a positive exercise test will have angiographically verified CAD.[2] Little evidence exists currently to support doing resting ECGs[3] or exercise tests[4] in patients without clinical evidence of coronary disease or cardiovascular risk factors.

Screening workers in high-risk occupations, such as bus drivers and airline pilots, has been advocated by many, but this is still controversial.[5] The result of this strategy would not be therapeutic intervention, but rather removing a person from a potentially hazardous situation.

If CAD screening is needed in an asymptomatic per-

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ABBREVIATIONS USED IN TEXT

CAD = coronary artery disease
ECG = electrocardiogram
PET = positron emission tomography

son, an exercise ECG test should be done, followed by scintigraphy if the exercise ECG test is abnormal.[4] Cost-effectiveness is higher in patients with coronary risk factors, increased age (>60 years), and in men. Arteriography should be done only if both noninvasive tests are positive.

Exercise Electrocardiographic Testing

The principle of stress testing is based on the characteristics of coronary artery flow. In normal coronary arteries, an increase in myocardial oxygen demand is paralleled by an increase in coronary artery flow. In coronary arteries with atherosclerotic stenoses, there is a fixed obstruction and an inability to increase flow, resulting in ischemia. The goal of the exercise treadmill test is to induce ischemia in a controlled setting, usually by attempting to reach a maximum exercise threshold, and to measure the physiologic response.

The exercise treadmill-ECG test is the oldest and most extensively used stress test. Patients selected for testing should be clinically stable and have an interpretable resting ECG. In general, the exercise treadmill-ECG test is indicated for men and women with atypical symptoms, patients with chronic stable angina, or those with a previous myocardial infarction to assess prognosis and functional capacity. Patients who cannot achieve sufficient cardiopulmonary stress because of respiratory difficulties or musculoskeletal problems or patients with poorly controlled hypertension, malignant arrhythmias, congestive heart failure, or substantial aortic stenosis should not undergo maximal exercise, and another form of stress testing should be considered. Similarly, patients with base-line abnormalities on ECG (such as left bundle branch block) should probably have exercise testing with scintigraphy or assessment of wall motion.

Various exercise protocols have been established. The most popular and thoroughly studied involves graded increases in treadmill speed and gradient angle every three minutes.[6] The test is terminated when a predetermined workload is met or when ST-segment and T-wave changes, blood pressure, heart rate, or symptoms preclude continuation. The hemodynamic and ECG responses to exercise in diseased and normal states have been well described and are generally regarded as valid and reproducible.[7] Wide variations in the sensitivity and specificity of exercise-ECG testing have been reported. In a large analysis, reported sensitivities ranged from 23% to 100% (mean, 68%) and specificities ranged from 17% to 100% (mean, 77%).[8] In the recent literature, an abnormal maximal exercise-ECG stress test (where the heart rate reaches 85% of maximum predicted for age) provides a sensitivity of 55% to 80% (mean, about 65%) and a specificity of 83% to 96% (mean, 85%) for the diagnosis of CAD in men.[7,9] Both the sensitivity and specificity are lower in women.[9] Single-vessel disease is especially problematic—most notably disease of the right or left circumflex coronary artery—with sensitivities ranging from 25% to 70%. In patients with angiographically documented multivessel disease, there is an increased mean sensitivity of 81% (range, 40% to 100%) with a decreased mean specificity of 66% (range, 17% to 100%).[8] Patients with hyperventilation syndromes, mitral valve prolapse, left ventricular hypertrophy, bundle branch block, preexcitation syndromes, electrolyte abnormalities (such as hypokalemia), and digitalis use commonly have false-positive ECG responses.

Variations in testing methods and ECG interpretation may explain the widely disparate sensitivities and specificities.[7] Computer-derived quantification of exercise-induced ECG changes may improve accuracy,[10,11] but it is not commonly used. Signs suggestive of notable exercise-induced ischemia, multivessel coronary artery disease, and an adverse prognosis include 2 mm or more of horizontal or downsloping ST-segment depression at 80 milliseconds past the J point on any ECG lead (V_5 is most commonly abnormal), the early onset of ST-segment depression (before stage II of the Bruce protocol or at a heart rate of <120 beats per minute), exercise-induced hypotension (a fall in the systemic blood pressure during exercise or a low peak systolic pressure with a heart rate of <130 beats per minute), an exercise-induced S_3 gallop, or an inability to reach an adequate heart rate (<70% maximum predicted for age) or workload (<5 mets or stage II of the Bruce protocol).[12,13] The definition of a "positive" test depends on all of these factors, but emphasis is often placed on the ECG changes alone. When reviewing results from exercise ECG testing, hemodynamic response, exercise duration, and symptomatic threshold should all be considered.

Exercise Thallium Testing

Thallous chloride Tl 201 is a radionuclide agent introduced in the 1970s and now used extensively in conjunction with exercise testing. Thallium 201-chloride is an intracellular cation that behaves similarly to potassium. Myocardial uptake of ^{201}Tl-chloride is proportional to regional myocardial blood flow and dependent on the presence of viable myocytes. After initial myocardial extraction, there is a continuous exchange of the radiopharmaceutical between the myocardium and blood pool. Ischemic myocardium that is viable will not initially take up ^{201}Tl-chloride but will eventually take up thallium with redistribution, typically within four hours. Thus, in an exercise-thallium study, the isotope is administered at peak exercise, and stress images are obtained immediately. Redistribution images are usually taken four hours later. The difference between ischemia and redistribution images can be enhanced by giving a second dose of ^{201}Tl-chloride before the redistribution scan is obtained.

Thallium images may be planar or tomographic (single-photon-emission computed tomography) and can be interpreted visually or with computer assistance. Exercise

TABLE 1.—*Characteristics of Tests for Detecting Coronary Artery Disease*

Source	*Technique*	*Sensitivity (Range), %*	*Specificity (Range), %*	*Advantage*	*Disadvantage*
Gianrossi et al, 1989[8]	Exercise treadmill testing (ETT)-ECG	68 (23-100)	77 (17-100)	Inexpensive while giving important prognostic information; less accurate in women	Requires clinical stability and interpretable ECG
Dilsizian et al, 1990[14]; Kaul et al, 1988[15]; Zaret and Wackers, 1993[16]; Friedman et al, 1982[17]	ETT scintigraphy with thallous chloride Tl 201	84	87*	Assists in locating ischemia; improved accuracy in women	^{201}Tl chloride is expensive and requires cyclotron use; exposure to isotope
Francisco et al, 1982[22]; DePuey and Rozanski, 1991[23]	Technetium Tc 99m sestamibi; Technetium Tc 99m teboroxime	Similar to ^{201}Tl chloride	Similar to ^{201}Tl chloride	Both agents can give assessment of ventricular function; can be locally produced; shorter half-life than ^{201}Tl	Relatively untested
Leppo, 1989[24]; Ranhosky and Kempthorne, 1990[25]; Nguyen et al, 1990[26]; Coyne et al, 1991[27]; Nishimura et al, 1991[28]	Dipyridamole-^{201}Tl chloride	86 (67-95)	70 (41-100)	Can be done in patients who cannot exercise	Contraindicated in patients with severe airways disease or taking theophylline; can cause substantial hypotension
Nishimura et al, 1992[30]; O'Keefe et al, 1993[31]; Abreu et al, 1991[32]; Ely and Berne, 1992[33]; Mason et al, 1984[34]; Hoffmann et al, 1993[35]	Adenosine-^{201}Tl chloride	88 (83-98)	85 (64-100)	Short acting; may be better in patients with LBBB	Contraindications as with dipyridamole; possible flushing, headache, chest, jaw pain, and bradyarrhythmia
van Rugge et al, 1993[40]; Gould, 1991[43]; Marwick et al, 1992[47]; Robertson et al, 1983[48]	Dobutamine scintigraphy	80-97	80-97	Scintigraphy can be done in conjunction with echocardiography; reported safe in patients with reactive airways	Limited experience at most centers
Ryan et al, 1993[54]; Picano et al, 1987[55]	Exercise echocardiography	88 (84-100)	80 (64-93)	Gives additional information of cardiac function, estimated pulmonary artery pressures; avoids radioactivity	Inadequate images in 10%; test quality is operator dependent
Zoghbi et al, 1991[56]; Marwick et al, 1993[57]; Marcovitz and Armstrong, 1992[58]; Sawada et al, 1991[59]; Cohen et al, 1991[60]; Pierard et al, 1990[61]	Dobutamine echocardiography	86-96	66-95	Avoids cumbersome treadmill or bicycle protocols; avoids need for exercise	Frequently causes chest pain, palpitations, or headache, making delivery of sufficient dose difficult
Gibbons et al, 1988[62]	Radionuclide ventriculography	85-90	90	Reported high accuracy and gives added information of cardiac function	High cost; reproducibility depends on preload and afterload; cannot be done in patients with LBBB, pacing, or arrhythmia

ECG = electrocardiography, LBBB = left bundle branch block

*Approaches 90% with computer-assisted imaging.

treadmill-thallium imaging has a sensitivity and specificity for detecting CAD of 84% and 87%, respectively.[14,15] Sensitivity approaches 90% with a quantitative computer-assisted analysis of images, without loss of specificity.[16] These data are collected from tertiary centers where considerable skill has been developed. In less experienced centers, accuracy may be lower, approaching that of exercise-ECG testing. Exercise-thallium testing does appear to improve accuracy over exercise-ECG testing in women,[17] and its use should be considered at centers experienced with this procedure. Exercise-thallium imaging has been shown to be effective in patients who can achieve only a moderate workload and where the exercise-ECG test is inconclusive, maintaining a sensitivity of 70% and a specificity of 95%.[18]

The use of thallium is problematic for several reasons. Thallium 201-chloride is a low-energy γ-emitter with a long biologic half-life. Because it has a rapid redistribution, imaging must be done soon after it is administered to obtain an accurate ischemic image. In addition, ^{201}Tl-chloride is expensive and generated by a cyclotron, usually requiring delivery from an outside distributor. Several factors have related to lowered sensitivity and specificity with thallium imaging: single-vessel disease (especially

circumflex artery), collateral formation, stenoses of less than 90%, antianginal drug therapy, left bundle branch block (abnormal septal imaging), cardiomyopathy (such as hypertrophic cardiomyopathy, dilated cardiomyopathy, and infiltrative diseases), and attenuation from the breast and diaphragm.

Technetium and Teboroxime

Technetium Tc 99m is a calcium analogue that has a higher photon energy (140 versus 70 KeV) and a shorter half-life (6 versus 73 hours) than ^{201}Tl-chloride. It can be produced from a local generator and the radiopharmaceutical agent safely given at much higher radioactivity doses than ^{201}Tl-chloride, thus providing images with much higher radioactive counts.

Technetium Tc 99m can be linked to a variety of agents and used as a marker of perfusion. Sestamibi is an isonitrile compound that is taken up by myocardium proportional to blood flow, but does not undergo redistribution. Teboroxime is a boronic acid derivative that is rapidly taken up by myocardium but also rapidly cleared. Thus, selecting either of these agents depends on how quickly after administration images can be acquired. For most practical purposes, teboroxime has such a short half-life that consistent image quality is difficult to maintain.[16] When used with exercise treadmill testing as stress, a small dose is given before exercise is started and gamma resting images are obtained. During peak exercise, a second larger dose is given and images again obtained and compared with resting images for areas of ischemia, infarct, or both.

The physical properties of ^{99m}Tc allow images to be acquired on the first pass through the ventricle. Gated images can provide an assessment of ventricular ejection fraction as well as perfusion. Several studies have shown that ^{99m}Tc-sestamibi and ^{99m}Tc-teboroxime are similar to ^{201}Tl-chloride in terms of sensitivity and specificity for detecting CAD.[19,20]

Dipyridamole

A considerable number of patients at risk for CAD are unable to do exercise tests. In many laboratories, 25% to 35% of all patients referred for myocardial perfusion imaging are given nonexercise stress testing. Pharmacologic perfusion imaging is now the test of choice in evaluating CAD in these patients. Pharmacologic agents can be used to induce ischemia or differential coronary flow. Agents such as dipyridamole or adenosine are coronary artery vasodilators and can augment flow in normal coronary arteries as much as fivefold. Flow in diseased coronary arteries does not appreciably increase in response to these agents. This flow differential can be detected when these agents are given in conjunction with perfusion markers such as ^{201}Tl or ^{99m}Tc compounds. When dipyridamole is given in large doses, it may rarely induce ischemia and wall-motion abnormalities that are detectable by ultrasonography, a principle used in stress echocardiography. It is important to remember, however, that dipyridamole induces pharmacologic vasodilation and redistribution of coronary blood flow and that ischemia is not usually present.

Dipyridamole, the most frequently used pharmacologic stress agent, is a nucleoside transport antagonist and blocks uptake and degradation of adenosine, leading to vasodilation in the coronary artery and systemic vasculature. In performing dipyridamole scintigraphy, a perfusion tracer (most commonly thallium) is administered about four minutes after dipyridamole infusion is completed. Dipyridamole-thallium testing has a reported sensitivity of 67% to 95% (mean, 86%) and a specificity ranging from 41% to 100% (mean, 71%).[21-23]

In most cases, dipyridamole produces a mild increase in heart rate (averaging 5 to 10 beats per minute) and a small decrease in systolic blood pressure (10 to 15 mm of mercury). About 50% of patients have side effects of chest pain, flushing, dizziness, headaches, or nausea.[24] Dipyridamole is contraindicated in patients with severe reactive airways disease and may provoke bronchospasm. Theophylline should be discontinued, when possible, before pharmacologic stress. Dipyridamole can cause substantial hypotension that can be reversed by giving aminophylline. Dipyridamole infusion has been associated with myocardial infarction and death in one large series,[25] leading some to advocate using shorter acting adenosine.

Adenosine

Adenosine can be administered directly and imparts a direct, short-acting vasodilator response to the coronary vasculature. Adenosine has possible advantages over dipyridamole including its direct action, short half-life, and vasodilatory effect. Doses can be adjusted easily, with titrated doses used for patients at higher risk for side effects. Adenosine-thallium studies have a similar diagnostic accuracy with a sensitivity of 88% (range, 83% to 98%) and a specificity of 85% (range, 64% to 100%) for the presence of CAD.[26-29] Directly comparing the use of exercise with that of adenosine in multicenter trials showed close agreement between the two techniques.[29,30] Adenosine-thallium imaging has not been directly compared with dipyridamole-thallium imaging.[23] Adenosine-thallium imaging may be superior to exercise-thallium testing in evaluating patients with left bundle branch block by apparently reducing septal artifact seen with exercise.[31] Dipyridamole use should have a similar effect.

Similar to dipyridamole, adenosine use is contraindicated in patients with severe reactive airways disease, and theophylline should be discontinued for 24 hours before testing. As with dipyridamole, caffeine consumption should be avoided the day before testing. Adenosine has substantially more side effects than dipyridamole, with a frequency of 79% by one report.[32] Side effects include chest, throat, or jaw pain, headache, flushing, and bradyarrhythmia. The infusion of adenosine is contraindicated in patients with baseline second- or third-degree atrioventricular block. Sick sinus syndrome is a relative contraindication. In patients without known atrioventricular nodal disease, first-degree atrioventricular block occurs in

10%, second-degree block in 4%, and complete heart block in less than 1%.[32] These quickly resolve when the infusion is discontinued.[23] In addition, adenosine may have intrinsic cardioprotective effects,[33] leading some to recommend its use over other agents.[31]

Dobutamine

Various catecholamines have been used to produce pharmacologic stress. These agents increase the heart rate, blood pressure, and contractility and thereby induce true ischemia. When coupled with an imaging agent such as ^{201}Tl-chloride, dobutamine provides results similar to exercise-ECG.[34] Dobutamine has also been used in conjunction with simultaneous wall-motion imaging by echocardiography,[35-38] ultrafast computed tomography,[39] and magnetic resonance imaging.[40] At low doses—5 to 10 μg per kg per minute—dobutamine increases the heart rate and force of contraction while causing a mild peripheral hypotension. In higher doses—more than 20 μg per kg per minute—the heart rate, contractility, and systemic pressure all increase and thus increase myocardial oxygen demand. In small studies using high-dose dobutamine, sensitivities of 80% to 97% and specificities of 74% to 90% have been reported.[34,37,41] Some have advocated using both scintigraphy and echocardiography with dobutamine infusion to enhance accuracy, especially in patients with left ventricular hypertrophy, in whom echocardiography appears to increase specificity.[37]

Side effects are frequent, occurring in 78% in one series, with chest pain, palpitation, headache, flushing, and dyspnea being common.[41] The maximum dose of 40 μg per kg per minute may need to be decreased in 25% of patients because of these symptoms. Ventricular ectopy is common with infusion, and nonsustained ventricular tachycardia and paroxysmal atrial fibrillation have been associated with dobutamine testing. Dobutamine infusion rarely causes bronchospasm, although dyspnea is commonly seen. It appears to be safe even with patients who have severe asthma.[42]

Positron Emission Tomography

Positron emission tomography (PET) offers another technique for evaluating coronary perfusion. A positron is a positively charged electron that is emitted from a nucleus during positron decay. The positron interacts with an electron and annihilates both particles, producing two 511-KeV γ-rays traveling in opposite directions. The γ-rays can be detected and images reconstructed in a manner similar to computed tomography. Various positron-labeled compounds can be used to assess coronary flow, the most common being rubidium chloride Rb 82 and ammonia N 13. In addition, labeled carbohydrates—such as fludeoxyglucose F 18—lipids, and amino acids can be used to assess myocardial metabolism. Gould has suggested that the clinical use of PET—particularly with generator-produced ^{82}Rb-chloride—is feasible in an office setting.[43,44] With a sensitivity and specificity for the detection of CAD approaching 96%, PET may prove to be cost-effective by reducing the number of angiograms.[45]

Echocardiography

Echocardiography can also be used to detect ischemia-induced regional wall-motion abnormalities that occur during stress testing.[46] Algorithms using both upright treadmill and supine bicycle ergometry, pacing, and pharmacologic stress in conjunction with two-dimensional ultrasonography have been successfully employed. Most wall-motion defects seen at peak stress persist as long as two minutes, allowing a window of time in which effective imaging can be done. In the case of exercise echocardiography, an adequate study depends on attaining maximum exertion and rapid imaging, which can be cumbersome, especially when using treadmill systems. Thus, stress echocardiography is operator-dependent, relying on qualitative interpretation. As many as 10% of patients will have inadequate images even in experienced centers. This limitation is countered by the versatility, portability, and relatively low cost of the test and the lack of ionizing radiation. In addition, the information obtained from a two-dimensional echocardiographic examination is an added benefit of this study. Of note, the specificity of stress echocardiography is decreased in all modalities when preexisting wall-motion abnormalities are present.

The most commonly used form of stress echocardiography employs imaging in conjunction with treadmill or bicycle exercise testing. For detecting CAD, exercise echocardiography has an overall sensitivity of 74% to 100% and a specificity of 64% to 93%.[46-53] Exercise echocardiography appears to be more sensitive, more specific, and more accurate than exercise-ECG testing alone.[51] A few studies have compared echocardiography with scintigraphy in stress testing, and good agreement has been seen.[52] Using both tests appears to increase sensitivity but lose specificity.[52]

Pharmacologic echocardiographic stress testing using both coronary vasodilators and sympathomimetics has been reported. High-dose dipyridamole infusion (0.84 mg per kg of body weight infused over 10 minutes) can induce ischemia and wall-motion abnormalities that may be detected echocardiographically. This has been reported to be comparable to other forms of stress testing for detecting CAD.[54] Similarly, adenosine echocardiography has been shown to have comparable sensitivities and specificities to stress scintigraphy,[55] although direct comparison has shown echocardiographic testing to be less sensitive.[56]

More experience has been reported with the use of dobutamine with echocardiography. Most institutions use a graded infusion to a maximum dose of 50 μg per kg per minute, or when 85% of maximum heart rate is reached. Complex ventricular ectopy can occur in 2% of cases and can be treated with short-acting β-blocker therapy. Sensitivities of 86% to 96% and specificities of 66% to 95% have been reported.[57,58] Excellent agreement was seen with scintigraphic techniques. As with exercise testing, the heart rate seems to correlate with diagnostic yield.[59] Compared with adenosine echocardiography, dobutamine echocardiography seems to provide a more accurate diagnostic response while maintaining a similar sensitivity to adenosine scintigraphy.[56] Low-dose dobutamine has been reported to

be useful in assessing myocardial viability and uncovering "stunned" myocardium after thrombolytic therapy.[60] Dobutamine echocardiography may prove to be useful in patients with previous infarction when seeking viable hibernating myocardium.

Myocardial perfusion can also be evaluated in an echocardiography laboratory. Administering contrast agents to the coronary circulation can enhance the ultrasonic signal reflected from the myocardium. Sonicated albumin microbubbles in the range of 6 to 8 μm are detectable by ultrasonography, particularly with the use of computer programs that subtract background and optimize image intensity. This technique is attractive because it is noninvasive and lacks ionizing radiation, but it does require further improvement in contrast agents and ultrasound instrumentation to image areas other than infarction.[61]

Radionuclide Ventriculography

Radionuclide ventriculography uses ^{99m}Tc-labeled erythrocytes to assess ventricular function and regional wall motion. Abnormalities of wall motion and changes in global ventricular function that result from exercise-induced ischemia can be detected using this technique. Studies have shown that patients whose left ventricular ejection fraction fails to increase with exercise have a worse prognosis than those whose ejection fraction does increase. Sensitivities of 85% to 90% and a specificity of 90%[62] for detecting CAD have been reported. This test may be limited by factors such as dependence on preload and afterload, an inability to gate cardiac cycles in the presence of arrhythmia, left bundle branch block, or electronic ventricular pacing, and the subjective interpretation of regional wall-motion abnormalities.

Future Directions

Other noninvasive techniques for defining coronary artery anatomy may prove to be useful in the future. Ultrafast computed tomography is reasonably sensitive for detecting coronary calcification that correlates with atherosclerotic disease.[63,64] Cine-magnetic resonance imaging can detect patent saphenous vein grafts, but because of heart motion, it has difficulty detecting flow in native coronary arteries.[65] Transesophageal echocardiography can often demonstrate proximal coronary anatomy and flow[66] and has been used in conjunction with pacing to show stress-induced wall-motion abnormalities.[67] None of these techniques can yet compare with the detailed anatomy provided by angiography.

Continuous ambulatory ECG monitoring has been employed to detect coronary artery disease. It has been particularly useful in detecting episodes of asymptomatic ischemia. A sensitivity of 66% with a specificity of 79% has been reported, which compares unfavorably with perfusion scintigraphy.[68] Specificity was markedly higher in patients in whom ST depression of greater than 1.5 mm was seen.[68] Measurement of the total daily ischemic burden (ischemia of more than 60 minutes' duration) has been touted as a prognostic factor, but survival studies in patients with stable angina have not shown this to be the case.[69] The role of ambulatory ECG monitoring currently appears to be as an adjunct to other noninvasive tests in providing information on duration and threshold of ischemic responses.

Strategies for the Diagnosis of Coronary Artery Disease

The assessment of anginal symptoms, age, sex, smoking history, blood pressure, serum lipid profile, and family history can help identify patients at high risk for CAD. Arguably, low-risk patients should not undergo stress testing at all because an abnormal ECG finding with high exercise tolerance is likely to be false-positive. Often, though, reassurance is a mitigating factor. In men at high risk with stable typical angina and normal exercise tolerance, a standard exercise treadmill test with ECG is the test of choice. Women with typical angina should similarly undergo exercise-ECG testing. A positive test is more likely to be false-positive, especially if symptoms are atypical. A second noninvasive test in these patients may be more cost-effective than proceeding to angiography. In other situations, the usefulness of the exercise-ECG test is lower: in patients unable to exercise (adenosine or dipyridamole scintigraphy), in patients with left bundle branch block or paced rhythm (adenosine or dipyridamole scintigraphy), and in patients with severe

TABLE 2.—*Suggested Stress Testing Based on Clinical Presentation—Which Test for Whom?*

Clinical Presentation	*Test*
Typical angina, normal ECG	Exercise ECG
Typical angina, women with positive exercise treadmill test (ETT), equivocal ETT, or abnormal baseline ECG	Exercise with thallous chloride Tl 201 or technetium Tc 99m sestamibi imaging
Typical angina, unable to exercise	Dipyridamole or adenosine scintigraphy
Atypical chest pain	
High exercise capacity	Exercise, with or without scintigraphy
Low exercise capacity or blunted HR response on antianginal therapy	Adenosine or dipyridamole
Poor exercise tolerance, moderate to severe bronchospastic airway disease, or both	Dobutamine echocardiography with or without scintigraphy
Large body habitus	Stress with ^{99m}Tc sestamibi imaging
Potentially unstable ischemic disease (recent ischemia or severe heart failure)	Adenosine scintigraphy
Left bundle branch block, paced rhythm, frequent ectopy	Adenosine or dipyridamole scintigraphy

ECG = electrocardiogram, HR = heart rate

bronchospastic disease where dipyridamole and adenosine are contraindicated (dobutamine echocardiography with or without scintigraphy) (Table 2). In large patients undergoing scintigraphy, technetium Tc 99m-sestamibi imaging may provide better definition than thallium perfusion scanning. In patients who are potentially unstable, adenosine scintigraphy may be advantageous because of adenosine's short half-life. In patients in whom the added information of wall-motion and left ventricular function are desired, stress echocardiography could be considered at centers familiar with the procedure. Similarly, stress radionuclide angiography could be done.

All noninvasive testing is qualified by the availability of testing modalities. All the information on test characteristics has been collected at large, usually tertiary care laboratories where operator experience is great. At centers where these tests are not commonly done, diagnostic accuracy may suffer.

As sophisticated tests are developed, the noninvasive assessment of coronary anatomy, coronary flow, and myocardial metabolism will evolve and could displace the methods available today. In the meantime, careful use of the many tests now available, used in the context of a particular patient's risk factors, can aid greatly in the assessment of patients with suspected coronary artery disease.

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Commentary

Preventive Medicine as a Component of the Office Visit—Is It Time for a Change?

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The physician-patient relationship has increased in complexity from Hippocratic concentration on treating an obvious disease to the tripartite office visit (Figure 1).

Physicians are inclined to take an exhaustive history and do a complete physical examination of every patient. Although this may be appropriate for inpatient admissions, during an office visit patients tend to resist shedding clothes when they cannot see an obvious relationship with their chief complaint. Physicians then tend to adjust their practice style, accommodating patients by addressing more narrowly their reasons for visits and their ongoing problems. This approach may satisfy patients, but physicians recognize that they are responsible for the whole person, not merely the current problem, and that they should include attention to preventive medicine as an integral part of every office visit.

After addressing the reason for the visit and any ongoing illnesses, time permitting, physicians would want to review the chart, noting when the patient last had a complete physical examination and comprehensive laboratory studies done, including a stool guaiac test, electrocardiogram, mammography, and immunizations. If the patient's chart indicates obvious deficiencies in these secondary preventive measures,[1] the patient might then be advised to schedule these examinations and procedures at a later date. At that time, physicians would also consider what other specific examinations and studies are indicated based on the patient's age, habits, and family history.

This aspect of the office visit is probably the most difficult and the most imperfectly practiced. Schwartz and colleagues, studying the practice habits of 2,610 internists, concluded that their use of disease prevention and health promotion activities falls short of expert recommendations.[2] A 1984 study of physicians' attitudes and practices regarding early cancer detection reported that primary care physicians' use of detection procedures did not conform with guidelines for the cancer-related checkup recommended by the American Cancer Society.[3] Reasons suggested for physicians' poor performance in preventive medicine include inadequate training in prevention,[4] lack of reimbursement for preventive services,[5] insufficient time, skepticism about the clinical effectiveness of preventive activities, and uncertainty regarding which services should be offered.[1]

In addition, physicians are trained in deductive reasoning, and, by contrast, the anticipatory, inductive reasoning used in preventive medicine seems ungainly. Physicians also tend to be overwhelmed by the many, at times conflicting, recommendations for early detection of disease. For example, Fleischer and co-workers proposed digital rectal examination beginning at age 40, and fecal occult blood testing and flexible sigmoidoscopy beginning at age 50 for detecting colorectal cancer, but noted that with reference to fecal occult blood testing, no controlled study has shown that screening the average-risk population will reduce mortality.[6] In contrast, Eddy recommends annual fecal occult blood testing and fiberoptic sigmoidoscopy every 3 to 5 years between ages 50 and 75 years, but stated that there is no direct evidence that the digital rectal examination reduces mortality from colorectal cancer.[7] The American Cancer Society added to the complexity by recommending that from age 50 sigmoidoscopy be done every 3 to 5 years if a patient has had two negative examination results a year apart.[3] Subsequently, this was changed to recommending sigmoidoscopy from age 50 every 3 to 5 years, based on advice of a physician.[8]

Recommendations regarding adult immunizations vary from giving influenza immunizations only to patients older than 65, with no booster diphtheria or tetanus vaccine given after adolescence,[8] to diphtheria-tetanus-toxoid every ten years throughout life,[9] and to complex protocols based on lifestyle and occupational exposure, including a broad spectrum of vaccines.[10-15] On a positive note, there is somewhat more uniformity regarding preventive care guidelines relating to breast and cervical cancer,[16,17] and recent medical literature contains more consensus recommendations,[18] culminating in the *Guide to Clinical Preventive Services,* with specific assessments of 169 interventions.[1]

Practiced as a part of the office visit, preventive medicine activities are flawed, but even more troubling is the

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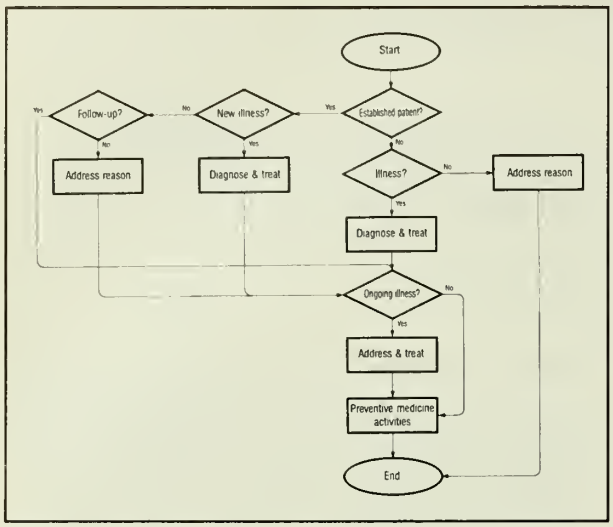

Figure 1.—The schematic represents the thought processes in an office visit in primary care medicine: the reason for the visit; attention to ongoing illness; and preventive medicine activities.

knowledge that because of intervals of up to several years between office visits in many cases, patients may receive no preventive medicine measures at all.

A Proposed Preventive Medicine Alternative

Because physicians are not including preventive medicine in most office visits, a variety of measures have been proposed to assist in that area. Written proposals for examinations and interventions have been grouped into "health protection packages" to be administered at different times during a person's lifetime.[19,20] Computer-generated reminders affixed to medical records have been shown to enhance compliance by physicians in ordering specific preventive care measures.[21-25] One study reported that although 80% of patients seen at least once in two years were compliant with a health maintenance program, a large number of inactive patients were not being reached. A computer tracking system could generate reminders for both patients and physicians at specified intervals.[26-28]

Computer software is being developed that will integrate billing systems, appointment schedules, patient records, and preventive medicine responsibilities. This software will incorporate preventive medicine recommendations, such as those developed by consensus by the US Preventive Services Task Force,[1] and, in addition to physician reminders, will automatically generate a letter to established patients every year on their birthday. This can be in the form of a birthday greeting followed by specific preventive medicine recommendations, based on age, sex, and increased risks due to family incidence of disease, personal history, and lifestyle patterns such as smoking. A patient will be advised to arrange for these examinations and a copy of the letter can be filed in the patient's chart as proof of the preventive medicine effort. While the physician remains responsible for following up on the written recommendations, the risk of overlooking a specific study is nearly eliminated by the computer's literal adherence to age- and sex-based algorithms. In effect, the bulk of the planning and recommendations for preventive medicine is transferred to an automated process that includes the files of all patients in the practice, not just those currently being seen.

Physicians should remain in control and responsible for the actions of the computer by reviewing each generated letter before signing and sending it to avoid errors or inappropriate recommendations. If patients choose to follow the recommendations made in the letter, they call to arrange an appointment. At this visit, the physician focuses primarily on preventive medicine services, moving directly to a comprehensive physical examination and a review of the results of the recommended studies, and secondarily addressing any ongoing medical problems. In response to any abnormalities discovered, physicians can suggest further studies, dietary changes, lifestyle alterations, and follow-up visits as needed.

Changing the format of the office visit in this manner (Figure 2) accomplishes two important objectives:

- Physicians are not distracted by trying to sort out what preventive medicine activities are indicated and are free to concentrate on a patient's current problems; and
- There is improved precision in the execution of preventive medicine activities.

Summary

A routine visit to a physician's office generally is composed of the reason for the visit; attention to ongoing medical problems; and preventive medicine considerations. A separate visit for preventive medicine activities can be helpful. A computer-generated annual birthday greeting to patients that suggests specific preventive medicine studies would result in a more problem-focused office visit and greater precision in the execution of preventive medicine activities.

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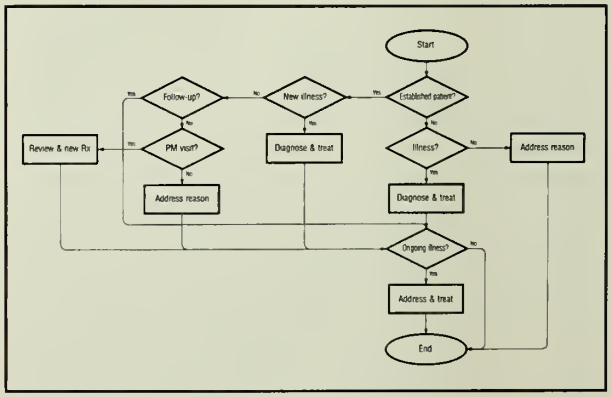

Figure 2.—This schematic diagram shows the primary care office visit without appended preventive medicine considerations, which have been segregated and computerized. Rx = prescription, PM = preventive medicine

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Commentary

How a Consumer Health Library Can Help Streamline Your Practice

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More consumers of health care are increasingly demanding satisfactory information about their medical problems. Although these demands are essential in helping patients make informed choices, they may overburden physicians. Consumer health libraries—medical libraries designed and staffed for the general public and patients—are part of the answer to this dilemma. They can amplify the essential medical information that cannot be given by a physician because of time burdens. They do not dispense medical advice or provide consultation. They do provide accurate and timely information that permits patients to become more knowledgeable about their medical problems.

Consumer health libraries resemble the medical libraries that physicians have known since they were medical students, but with one crucial difference. They are planned and staffed not primarily for physicians, but for patients and the general public. Despite this, they can also assist physicians in various important ways:

- They provide accurate and timely information about medical problems and can guide patrons in doing necessary research.
- They can furnish specific information to patients at a physician's request.
- When patients do not fully comprehend what their physician has told them, particularly if they have a complicated medical problem or an illness that seems to be life-threatening, the library gives them the opportunity to become better informed in a less threatening environment and to ask more pertinent questions of their physician.
- The information given to patients may limit a physician's tort liability. Many malpractice suits can arise when the patient and the family do not fully comprehend a recommended course of treatment, its limitations, and its risks. The library staff guides the patient and family to appropriate reading to help overcome this problem. The information can be copied and taken home for rereading.

Some critics of consumer health libraries feel that they dispense information that is not always objective. No studies could be found that address this question, so the issue cannot be resolved at this time.

The heart of a typical consumer health library is its voluminous clipping file containing accurate and up-to-date information on almost any conceivable medical subject. Because this material is regularly culled from medical journals, newsletters, magazines, and newspapers, it is always current. The culling is usually done by volunteers, which makes it cost-effective. Physicians may also find the clipping file useful and less expensive than a MEDLINE search.

A consumer health library's shelves contain stacks of books and journals, including an assortment of standard medical texts and periodicals. The library also has a collection of books and newsletters written specifically for the public to make medical information more understandable.

Many libraries now have educational video sections with standard video cassettes and interactive videos. An even newer service is a user-friendly interactive computer program, such as the Health Reference Center from Infotrac. A patron can enter the name of a medical condition on the keyboard. Appropriate references then appear on the monitor with directions as to how more information can be obtained. This allows unlimited searches without the time and expense of an on-line computer service.

Consumer health libraries have computers that can be used for a search of MEDLINE, PDQ, or other MEDLARS databases. A librarian will usually have to conduct these searches. Recently developed gateway programs are making these data bases more accessible to the general public.

Some libraries offer a free lecture series. Physicians are invited to give brief talks and to answer questions about a topic pertaining to their specialty. In addition to providing useful information, this may also help physicians receive new patients from the audience.

Consumer health libraries should be staffed by medical librarians, perhaps with assistance from nurses and other volunteers. Persons with this training are relatively scarce, however, and alternative solutions are often

(Notkin H: How a consumer health library can help streamline your practice. West J Med 1994; 161:184-185)

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Reprint requests to Mrs K. D. Proffit, Sutter Resource Library, Box 160727, Sacramento, CA 95816.

necessary. Libraries usually are open without charge to the public residing in the area. Memberships for others may be offered at a cost of $10 for senior citizens and as much as $250 for businesses. Members obtain free mailings and the use of books and videos. They also receive discounts for on-line computer searches.

The consumer health library movement has caught on fairly slowly and spottily in the past decade. There are now at least 25 libraries nationwide, scattered over about 12 states. In addition, an unknown number of hospitals are developing their own libraries, often dealing with only one subject, such as cancer or aging. There is no satisfactory nationwide list of consumer health libraries. The list included here, compiled from several sources, is as complete and as accurate as possible. There are almost certainly many more. Those associated with public library systems are difficult to identify.

Physicians who appropriately refer their patients to such a library or attempt in concert with hospitals and other community health agencies to organize one will find that their efforts will reap notable savings in energy, exposure to liability, and, most important of all, time.

ARIZONA

W.O. Boswell Memorial Hospital
First Edition
13101 N 103rd Ave
Sun City, AZ 85351
(602) 974-7848

CALIFORNIA

Alta Bates-Herrick Hospital
Vintage Health Library
2001 Dwight Way
Berkeley, CA 94704
(510) 540-4475

California Pacific Medical Center
Planetree Resource Center
2040 Webster St
San Francisco, CA 94115
(415) 923-3680

Gould Medical Center
Gateway Health Library
500 Coffee Rd, Suite D
Modesto, CA 95335
(800) 52-GOULD

Kaiser Permanente Medical Center
Health Education Center
280 W MacArthur Blvd
Oakland, CA 94611
(510) 596-6150

Kaiser Permanente
Learning Center
13652 Cantara St
Panorama City, CA 91402
(818) 375-3018

Los Gatos Medical Resource Facility
815 Pollard Rd
Los Gatos, CA 95030
(408) 866-4044

Mission Hospital Regional Medical Center
Consumer Health Information Center
27700 Medical Center Rd
Mission Viejo, CA 92691
(714) 582-2919

San Jose Medical Center
Planetree Resource Center
98 N 17th St
San Jose, CA 95112
(408) 977-4549

Stanford University Hospital
The Health Library
248 Stanford Shopping Center
Palo Alto, CA 94304
(415) 725-8400

Sutter Resource
PO Box 160727
Sacramento, CA 95816
(916) 733-3880

Valley Care Medical Center
Valley Care Health Library
5575 W La Positas Blvd, Suite 120
Pleasanton, CA 94588
(510) 734-3315

Veterans Affairs Medical Center
Patient Education Resource Center
4150 Clement St
San Francisco, CA 94121
(415) 221-4810, x3477

FLORIDA

James A. Haley VA Medical Center
Patient's Library
13000 Bruce B. Downs Blvd
Tampa, FL 33512
(813) 972-2000, x7531

ILLINOIS

MacNeal Hospital
Consumer Health Information Service
3249 Oak Park Ave
Berwyn, IL 60402
(708) 795-3089

MICHIGAN

Battle Creek HealthSystem
HealthNetwork
80 N 20th St
Battle Creek, MI 49015
(616) 964-5616

Bronson Methodist Hospital
HealthAnswers
252 E Lovell
Kalamazoo, MI 49007
(616) 341-6318

Catherine McAuley Health System
McAuley Health Information Library
PO Box 995
Ann Arbor, MI 48106
(313) 712-5177

MISSOURI

Consumer Health Information Research Institute
3521 Broadway
Kansas City, MO 64111
(816) 753-8850

NEW HAMPSHIRE

Hitchcock Clinic Pregnancy Resource Center
2 Maynard St
Hanover, NH 03576
(603) 646-7860

OREGON

Good Samaritan Medical Center
Family Resource Center
1015 NW 22nd Ave
Portland OR 97201-5198
(503) 229-7348

TEXAS

Wadley Regional Medical Center
Wadley LifeSource
57 Central Mall
Texarkana, TX 75501
(214) 793-5433

WASHINGTON, DC

Providence Hospital
Center for Life Aging Resource
1170 Varnum St
Washington, DC 20017
(202) 269-7075

WASHINGTON (STATE)

King County Library System
Bellevue Regional Library
(No formal health library, but a great deal of consumer health material is available.)
1111 110th Ave NW
Seattle, WA 98004
(206) 450-1760

Editorials

Do You Have a *Campylobacter* in Your Future?

A SHORT TIME AGO, *Campylobacter jejuni* was not a well-recognized pathogen. This curved, gram-negative rod was considered an esoteric microbe associated with veterinary diseases and occasional human cases of bacteremia or septic abortion. As culture methods for campylobacters improved, the recognition of the important role of these microorganisms in causing human disease also increased. In the article by Peterson elsewhere in this issue of the journal, the impressive scope and magnitude of clinical disease produced by *C jejuni* are reviewed.[1] In addition to its major role in the causation of commonly acquired infectious diarrhea among persons in developed countries, several important observations have emerged. *Campylobacter jejuni* is now appreciated as an important cause of morbidity and mortality in young children in developing countries and in immunocompromised persons in developed countries, and it also may be the most important trigger of the Guillain-Barré syndrome in this country and in others.[2-4] Most recently, *C jejuni* has been implicated as a cause of acute motor axonal neuropathy, a paralytic disease that has affected thousands of Chinese children.[5,6]

Despite the substantial burden of illness imposed by *C jejuni* infections, many clinical microbiology laboratories still do not look for campylobacters in stool specimens submitted for routine culture. Furthermore, a growing number of "atypical" campylobacters—other *Campylobacter* species and species within the *Arcobacter, Helicobacter,* and *Wolinella* genera—are increasingly implicated in human disease,[7-9] but they are fastidious organisms and difficult to culture. Identifying these organisms requires special culture media or filtration methods; unless they are specifically searched for, they will not be found. Consequently, new associations of disease with these unusual or difficult-to-grow microorganisms may be missed. When a new pathogen is identified, such as *C jejuni* or *Legionella pneumophila* serogroup 1, an explosion of discoveries of other related species frequently ensues. In the current medical cost-containing environment, however, filtration techniques for campylobacters may seem frivolous when the yield often is low.

A brief consideration of the epidemiology of *Campylobacter* infections narrows the group of patients with diarrhea in whom a search for campylobacters is indicated. Persons in whom diarrhea develops after they have been in a hospital more than 72 hours are unlikely to be infected with *C jejuni*—or *Salmonella* or *Shigella* species, for that matter[10]—and routine cultures should not be done. In contrast, *Campylobacter* cultures should be done on persons who are at high risk for being infected with these organisms. These high-risk persons include outpatients who present with fever and diarrhea (especially diarrhea that is bloody or contains leukocytes) and who are far more likely to have a bacterial cause of their illness. Infections with *Campylobacter* species may mimic appendicitis in some patients; identification of campylobacters in stool specimens could eliminate the need for surgical intervention in some of these patients, although culture results may not be available in time to prevent many laparotomies. Similarly, persons infected with the human immunodeficiency virus (HIV) or other immunocompromised persons with diarrhea may be infected with campylobacters and related organisms, even if the symptoms are chronic.[11] Other persons at high risk for *C jejuni* infection include travelers to developing countries and persons with possible occupational or recreational exposures to campylobacters in whom diarrhea develops. Persons suspected of having inflammatory bowel diseases should have stool cultures for campylobacters and related organisms as a routine part of their diagnostic workup. The cost of campylobacter cultures is minimal when compared with the medical and social costs associated with a false diagnosis of idiopathic inflammatory bowel disease.

Campylobacter jejuni infections are most likely prevented by adhering to basic food safety rules. As highlighted by Peterson, *C jejuni* usually is not transmitted from person to person, but is acquired from foods of animal origin. Although unpasteurized milk is the most common cause of outbreaks of *C jejuni* infections,[12] sporadic cases—which account for the lion's share of disease—are most often associated with the consumption of poultry and poultry products.[13,14] Reducing *Campylobacter* species contamination of poultry and poultry products will diminish the burden of human disease. For consumers, because *C jejuni* is easily killed by heat, thorough cooking and avoidance of cross-contamination of utensils (such as cutting boards) probably could reduce the rate of *C jejuni* infections. Special vigilance for preventing *C jejuni* exposure is warranted in patients with HIV infection in whom more severe and chronic infections with *C jejuni* may develop than in immunocompetent persons.[15,16] *Campylobacter jejuni* infections among patients infected with HIV are clinically apparent more than 30 times more frequently than in the general population.[11] This implies that *C jejuni* is in wide circulation but that the inoculum usually encountered is insufficient to cause illness in a normal host.

Despite the ubiquity of *C jejuni* and the frequency of both symptomatic and asymptomatic infections, the pathogenesis of *C jejuni* enteritis remains poorly understood. Because many patients with *C jejuni* infections experience watery diarrhea and because *C jejuni* isolates have been reported to be enterotoxigenic,[17,18] this mechanism was thought to be important. More recently, however, the role of enterotoxins in the pathogenesis of *C jejuni* enteritis has been called into question for the following reasons:

- Enterotoxin production cannot be detected in vivo;
- Patients with *C jejuni* infection do not have a serologic response to cholera toxin[19]; and
- Most patients have fever, bloody stools, and fecal leukocytes, which are not caused by choleralike enterotoxins.

The pathogenesis of *C jejuni* infection more likely involves cytotoxin production or direct bacterial invasion and proliferation within the intestinal epithelium. Both natural and experimentally induced infections typically induce serum- and mucosal-specific antibody responses,[20] and the increased frequency of *C jejuni* bacteremia in persons with hypogammaglobulinemia[21,22] suggests that humoral responses play a key role in limiting the scope of infection. The increased frequency of chronic *C jejuni* infections in HIV-positive persons suggests, however, that cell-mediated immunity also may play a protective role.

Humoral immune responses also may have deleterious effects. Cross-reactivity between antibodies to *C jejuni* and host structures may be responsible for a number of other postinfectious illnesses including Reiter's syndrome and Guillain-Barré syndrome. Identifying particular serotypes or other strain characteristics capable of triggering this type of immune response is necessary so that control and prevention strategies may be devised.

In the past 20 years, *C jejuni* has become established as an important cause of enteric infection; the rheumatologic and neurologic sequelae of *C jejuni* infections also are becoming increasingly well publicized. But *C jejuni* infections continue to be underconsidered by physicians and underdiagnosed by microbiology laboratories, and cases are underreported. Despite the fact that campylobacters are detected in stool specimens of patients with diarrhea more frequently than *Salmonella* and *Shigella* species combined when they are looked for,[10] states continue to report cases of *C jejuni* infections at a far lower rate.[23,24] Further efforts are needed to increase campylobacter surveillance and to investigate the pathogenesis of the sequelae of campylobacter infections. Such studies are likely to shed light on the expanding roles these organisms play in causing human disease.

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Are We Plumb Crazy?

LEAD (in Latin, *plumbum*) was used in some of the earliest inventions, including the forging of rigid metal implements, in medicinals, and in cosmetics. Its use was a key to the advancement of some civilizations and perhaps contributed to the demise of others.[1] Today lead lingers in the environment as an inauspicious consequence of human achievement. Had we known, in the making of that first leaded utensil, what poisonous course would be weaved for humankind, we may have tended our progress more cautiously. Yet in 1990, more than 1,275,000 metric tons of lead were used annually in the United States.

The toxicity of lead has been known since antiquity and was described by Nikander and other ancient writers. Premodern descriptions of lead toxicity focused only on occupational exposure. The classical clinical effects of lead and other metals were recognized in potters, painters, and miners. That it could afflict persons outside the trades was not reported until the late 1800s, however. The original cases of childhood lead poisoning due to lead-based paint were uncovered in Queensland, Australia, when paralysis, colic, convulsions, and optic neuritis were de-

scribed.[2] From this point on, it was clear that lead had become an environmental toxin. Cases of chronic nephritis that resulted from earlier childhood exposures were later described in the Queensland populations reported on by others. In the United States during the 1930s, increasing reports of urban childhood lead poisoning appeared. Despite the introduction of chelation therapy, morbidity and mortality remained high. In the 1960s mass screening programs revealed prevalences as high as 20% to 45% of children having blood lead concentrations greater than 40 μg per dl. In 1971, the Lead-Based Paint Prevention Act ordered the amount of lead in residential paints to be reduced to 0.06% following a Consumer Product Safety Commission study and also instructed the Office of Housing and Urban Development to study abatement measures. While new paint was to contain "safe" amounts of lead, the problem of lead in existing buildings began to perplex society.

The other major ubiquitous source of environmental lead was leaded gasoline. Although leaded gasoline had been manufactured and sold since 1923, rising blood lead concentrations and contamination of air and food convinced the Environmental Protection Agency to phase out lead in gasoline beginning in 1973. Societal and governmental recognition of increasing environmental exposure, leading to the regulation of lead in paints and gasoline, has resulted in a substantial reduction in exposure. Those of us growing up in the 1940s, 1950s, and 1960s had childhood daily doses and blood lead concentrations three to five times those of today's children. Indeed, most of the US urban population during those years would be judged lead "poisoned" by today's pediatric standard (>10 μg per dl). As blood levels have dropped with decreasing air and food concentrations, concern for lead-exposed persons has spread from medical and pediatric specialists to epidemiologists, public health officials, and preventive medicine physicians. The effects of lead exposure at today's environmental concentrations are insidious and subclinical, but still very real.

Elsewhere in this issue of the journal, Landrigan and Todd review the current understanding of lead exposure, its subtle effects, and newer public health issues.[3] The effect and magnitude of low levels of lead on neurobehavioral and cognitive functions in children are robust among both prospective and cross-sectional epidemiologic studies. Many possible confounding socioeconomic factors have been addressed. In individual persons, the assessment of neurobehavioral and cognitive impairment attributable to low levels of environmental lead is currently impossible because of a lack of simple measures, large individual variability, and multifactorial causes. Therefore, the screening of blood lead concentrations would lead to interventions that may ameliorate exposure and future effects. Blood lead screening is now mandated in many states, and many public health programs are following the guidelines provided by the Centers for Disease Control and Prevention (CDC). Iron deficiency produces strikingly similar neurobehavioral and cognitive effects in children, however.[4] Mild iron deficiency states have not been well studied, but may be prevalent in the same settings of lead exposure. Lead and iron interact environmentally, toxicokinetically, and toxicodynamically. For example, in low socioeconomic strata, decreased iron in the diet is likely to result in greater lead absorption and lead can compete with iron for ferrochelatase. It was recently shown that cognitive scores in children improved slightly after lead chelation and not after iron supplementation, but were significantly correlated with initial ferritin concentrations (about 40% were ferritin deficient) and not with initial lead concentrations.[5] These findings are consistent with either the known irreversible effects of iron deficiency on cognitive development or the earlier effect of lead. Although most of the major epidemiologic studies associating lead with neurobehavioral and cognitive outcomes have not examined iron stores as a covariate, an opportunity should not be missed in lead screening programs to prevent the possible irreversible effects of iron deficiency. Currently, the CDC recommends hemoglobin and iron measurements only as a follow-up evaluation to elevated blood lead concentrations. Initial testing is recommended.

Landrigan and Todd force us to consider some disturbing new questions regarding lead screening. Should every child in the United States be screened for blood lead concentrations of higher than 10 μg per dl, the current CDC recommended level of concern? Although a greater prevalence of elevated blood lead concentrations exists in inner-city children, many exposures are unique and site specific rather than environmentally ubiquitous. Herbal and traditional medicines, lead-glazed ceramic ware, lead-containing toys, molding and casting of lead in crafts and hobbies, and the renovation of old buildings in gentrified areas are some of the contemporary sources of pediatric lead poisoning. A number of screening programs have shown low prevalences of elevated blood lead levels in many suburban settings. For example, in Texas 8% of 43,436 children had blood lead concentrations of greater than 10 μg per dl and 0.8% had levels greater than 20 μg per dl. A more alarming prevalence was demonstrated in 4,196 inner-city children of Washington, DC, in which 18.6% had blood lead levels higher than 10 μg per dl and 1.6% higher than 25 μg per dl.[6,7] Given the variation in prevalence found for elevated blood lead levels in children, more focused screening will evolve as high-risk populations are identified. Screening and preventing exposure in populations at risk should continue because the long-term cost-effectiveness is likely to be greatest in the areas of educational and behavioral remediation.[8] Frontline health care professionals are often reluctant to carry out public health policies when they cannot see the fruits of their labors. Physicians can be encouraged to screen children if public health departments show how lead-induced disease and its interventions compare with other childhood illnesses. In essence, with feedback, health care workers will sense they are making a difference.

At what level do we stop worrying about lead? The balance of the cost-benefit equation is now changing somewhat as we confront possible and costly remedies.

Public health workers are recommending behavioral modification, dietary changes, repeated screening, and calcium and iron supplementation. While such recommendations have a good theoretical basis for their possible benefits and are considered precautionary and otherwise benign, outcomes research has yet to be done that establishes these interventions as efficacious. Abatement, though costly, is also a possible remedy. With the adoption of the Title X Lead-Based Paint Hazard Reduction Act of 1992, a $4 billion abatement industry has been launched. This industry will be highly regulated in that it creates a new occupational work exposure to be monitored by the Occupational Safety and Health Administration. Also, the disposal of the voluminous amounts of generated hazardous waste will be expensive. A recent randomized trial of soil and interior dust abatement showed modest declines in blood lead concentrations (about 2 μg per dl), but the authors concluded that such intervention would not produce substantial clinical or public health benefits.[9] On the other hand, abatement if done carelessly may reintroduce lead into a child's environment and reduce the efficacy of this intervention. If we wait for old houses containing lead paint to outlive their usefulness, what damage will be done to children in the interim? If we remove lead-contaminated paint now and bear the cost, how reliable, efficacious, and safe will this process be? Only limited studies exist. There is a great need for outcomes research on these topics.

Of great concern is that some practitioners are chelating at lower and lower blood lead concentrations. Standard chelation protocols have not been studied for their efficacy and long-term safety at blood lead concentrations of less than 45 μg per dl (one study is in progress), yet few alternative, effective, and economical interventions have been proved for blood lead concentrations in the 10- to 45-μg-per-dl range. The echo of "do no harm" looms over this approach. Recent work suggests that redistribution to other target organs may occur with several commonly used chelators.[10,11] Again, outcomes research on such interventions is needed.

One of the most important new developments in our understanding of lead toxicity, which is discussed by Landrigan and Todd, is the use of x-ray fluorescence of bone to determine lead content. With this new tool, we have a new measure of lead exposure or dose.[12] If a person had exposure to a constant amount of lead throughout their lifetime and internal exposure was well equilibrated with the deposition of lead in bone at all times, a blood concentration might be indicative of body burden or past exposure. Such is not the case, however. Lead exposure changes throughout our lifetime, and the physiologic processes that handle lead in the body change from infancy through old age. Therefore, blood lead concentrations tend to reflect recent exposure. Because a portion of all lead passing through the body is deposited in bones, the concentration in bone will represent a measure of lifetime exposure or "pass-through dose," an integrative measure of the amounts of lead seen by the soft tissue target organs. This has been validated in studies where integrated measures of past exposure are shown to correlate well with bone lead levels as measured by x-ray fluorescence.[13] Because most of what we know about the effects of lead has been benchmarked to blood lead concentrations, a new view of lead's effects in relationship to bone concentrations will soon be available. In all likelihood, bone lead concentrations will be reflective of chronic injury to the central and peripheral nervous system, the kidneys, and the reproductive system. On the other hand, biologic processes with high turnover and repair (reversibility) are less likely to correlate with cumulative past lead exposure (hematologic, vasopressor, and gastrointestinal effects), where blood lead levels will remain indicative.

Landrigan and Todd question whether workplace standards of lead exposure need to be scrutinized and tightened. This, no doubt, will come to pass, particularly as scrutiny of the workplace and biologic monitoring become more convenient and practical. Currently, it is estimated that less than 10% of workplaces with lead exposures have effective surveillance programs. If blood lead testing were to become more convenient, both pediatric and occupational populations would benefit. The CDC is currently sponsoring cooperative agreements and grants to promote the development of portable blood lead testing devices. Landrigan and Todd suggest that the blood lead standard be lowered from 50 to 10 μg per dl. The foundation for this recommendation is the mismatch between 50 μg per dl and the much lower concentrations associated with lead effects; however, only the mild vasopressor effect of low blood lead concentrations in some populations would support a standard as low as 10 μg per dl. Lowering the standard to 10 μg per dl, however, is justified on the basis that workers should not have exposures that exceed the environmental background for the general population.

At least several million children may be at risk for some loss of their future cognitive potential, and more than a million workers are employed in lead-related jobs. Our body burdens of lead are still 100-fold higher than those of ancient peoples. Unfortunately, we assimilate our environment, and lead will always be present. Are we "plumb crazy"? As the effects of current body burdens are compared with future lower backgrounds, no doubt other effects of lead may be discernible.

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Office-Based Prevention—How Can We Make It Happen?

THE ARTICLE BY Dr James in this issue of the journal stimulates discussion about the best ways to encourage the use and delivery of clinical prevention services in office practice.[1] The author describes a computer-based method of enhancing prevention, sending yearly reminders to devote a visit to patient-appropriate prevention and screening activities. The prevention activities will be those deemed age- and gender-appropriate by one of several expert bodies,[2,3] with modifications based on patient and physician preferences.

How might such a method work in practice? That depends on whether patients and physicians want to practice prevention and on what they expect from their efforts. Physicians express general agreement with expert guidelines on prevention,[4,5] and patients say that they are willing to practice prevention.[6,7] Still, few preventive services are provided at the recommended levels. Only a third of women receive timely and appropriate breast cancer screening services, and about half to two thirds are appropriately screened for cervical cancer.[8-14] Of high-risk candidates for influenza, in any year only 20% receive immunization,[15] and only about half of all smokers report that they have ever been told to stop smoking or to smoke less by a physician.[16] Even among relatively affluent, well-insured children, only 45% of two-year-olds and 55% of six-year-olds are current for all recommended immunizations.[17] Other prevention services have similar or even lower rates of appropriate use.[11]

There are a variety of reasons for our failure to deliver prevention services, attributable to the physician, the patient, or the system in which the encounter occurs.[18] Time, both the patient's and the physician's, has been recognized as a barrier.[17-22] Physicians in a faculty adult primary care practice spent just 8% of their time in prevention, 60% of this in breast and cervical cancer screening and influenza immunization.[23] This brief period includes time spent in dedicated prevention visits and, more often, time borrowed during illness visits.

Attitudes of physicians and patients may also form barriers to prevention. Physicians and patients may find it difficult to justify expending time, money, and effort on preventing illness that seems unlikely or distant. Physicians who are not preventionists[24] by training may find remote outcomes or epidemiologically-based predictors unsatisfying.[24] Better personal health habits practiced by physicians have been shown, for male physicians, to lead to better prevention care for their patients.[25] The Women Physicians' Health Study, a study of the health and counseling practices of 10,000 women physicians being conducted by one of the authors (E.F.), should help clarify whether this is also true for women physicians.

Physicians may also forget to address prevention with their patients,[21] and applying risk profiles to the recommended schedules can make providing comprehensive prevention services even more complex. For example, the US Preventive Services Task Force (USPSTF) specifies 60 target conditions for prevention and 169 age- and gender-specific preventive services. One study used a computer-based algorithm of USPSTF rules based on age- and gender-specific risks to count an average of 24.5 recommendations for 230 adult ambulatory patients.[26] It is a difficult task to enumerate all appropriate recommendations and harder yet to complete them. Additionally, the logistics of prevention, such as the scheduling of mammograms, often done off-site from physicians' offices, provide further obstacles.

Physicians and patients may base decisions on patients' ability to pay or the availability of insurance reimbursement for preventive services.[13,22,27] Medicare, whose lead is often followed by private insurance companies, currently pays for only four preventive services: mammography, Pap smears, pneumococcal immunization, and hepatitis B immunization.[28] Hillary Rodham Clinton, in testimony to Congress about the Health Security Act, reported that she had to pay out-of-pocket for her last mammogram before her husband's inauguration. Even when physicians' and patients' knowledge, attitudes, and schedules allow for a preventive intervention to occur, restrictive and short-sighted financial policies may provide an enormous impediment to implementation.

Physicians have been overwhelmed with preventive guidelines, many conflicting,[7,29] and often are uncertain of appropriate screening schedules and procedures, leading some to underuse them. This may have changed,[30] however, with the publication of the USPSTF "Guidelines to Clinical Prevention Services" in 1989. That report, which included evidence-based recommendations and rankings of the effectiveness of available prevention services, has been widely disseminated. A new USPSTF report and the upcoming "Put Prevention Into Practice" campaign of the Department of Health and Human Services Office of Disease Prevention and Health Promotion may further improve physicians' knowledge about and confidence in the value of clinical prevention services.

How might an anniversary letter suggesting a prevention visit address these obstacles? A visit devoted solely to prevention and disease screening might relieve some of the time pressure felt by clinicians to work on established medical problems, though there is no guarantee that even

in such a visit the patient or the physician would focus solely or even primarily on prevention tasks. The same computer that generates the anniversary letter might also be used to produce educational materials, based on patient characteristics, that inform and prompt both the patient and the physician about recommended services, an approach that some feel will be powerful.[12,31] A recent trial showed that mailed reminders tailored to specific patient risks and concerns can increase mammography screening.[32] In another, patient nonresponders to cholesterol screening reminders stressed the need to personalize the message.[4] Computers can be made to be less forgetful than physicians or patients, removing that obstacle, at least while the reminder letter is in front of the physician. In time, the same system that is used to create and mail an anniversary letter may also aid in scheduling prevention services. All of these concerns may be helped, in part, by Dr James's suggested approach.

The hardest problems remain, however. Physician time for screening for breast and cervical cancer required 10.5 minutes for each mammogram and 11.5 minutes for each Pap smear completed just to counsel the patient, schedule the test, look up results, and do the Pap smear or the clinical breast examination.[23] Screening for just two diseases took up to 22 minutes, and while this may not be required every year, a single hour may not suffice for the 60 conditions on the USPSTF schedule. Reimbursement also remains a problem, though payment in the form of a periodic preventive health visit fee has been suggested.[33] Finally, no current scheme, computer-based or not, can adequately account for the preferences of patients and physicians about the prevention of distant diseases. These would seem to be the most difficult issues about office-based prevention services to resolve, and they are not likely to be much affected by an anniversary appointment devoted to prevention. Ultimately, Dr James's suggestion deserves to be debated and its value demonstrated, as does any thoughtful attempt to promote disease prevention in an era of increasingly constrained health resources and increasing emphasis on prevention.

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Correspondence

Interpreting Toxic Intern Syndrome

To the Editor: As a medical school graduate of 33 years and a physician in private practice for 24 of those years, I take strong exception to Dr Dyer's conclusions in her commentary in the April issue.[1] My interpretation of her basic conclusion is that we are either stuck with a terrible system—her description—or we must bring unlimited resources to have something more to her liking. She yearns for the coming years of private practice or an academic life. I have news for her. It gets worse. She will be called increasingly to spread limited resources among unlimited demands for them. The whole thesis of managed care is to justify and limit requests for health care. Physicians have to learn where their efforts will be of benefit and push hard in that area while realizing that not everything can be done and that with some patients, much effort will go for nought.

I hope that Dr Dyer survives (or has survived) her internship and will go on to enjoy medicine in this less than perfect but still very interesting world where she can make a difference, even if it is not as great a one as she would like.

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* * *

Dr Dyer Responds

To the Editor: I was surprised at the dichotomous reaction to my article. On the positive side, my fellow interns, residents, and hospital staff generally agree with the sentiments I expressed and claim that I have captured the "internship experience." They appreciate that someone has finally put into writing the common feelings of a resident's daily life. One of my former residents, now faculty, plans to make the article required reading for his medical students. I have also received letters from other physicians who assure me that things do get better in private practice.

On the negative side, I have been questioned as to whether I should even have gone into medicine. Upon returning to the Veterans Affairs hospital I was asked, "How can you work here when nothing has changed?" Another physician told me, "It's not a toxic intern syndrome, it's reality." I find that those who react negatively to my comments are misinterpreting them or missing the point.

I wrote "Toxic Intern Syndrome" at the end of my year of training in internal medicine in Fresno to gain some perspective, put into writing what was going on around me, and start questioning the process.

The issues I raised are those faced daily by house staff and primary care professionals who contribute the bulk of the medical treatment in many areas for the homeless, indigent, veterans, and immigrants. My purpose was to get people to take notice, to remember and begin thinking about the problems. I hope that someone else reading the article will find the solutions to the problems. Without questioning there is no change.

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The Ethical Versus the Legal

To the Editor: Dr De Ville's commentary in the May, 1994, issue[1] makes the point rather well that ethical and legal issues should be separated when discussing a bioethical "hard case." The difficulty comes when a case progresses from discussion to action. Physicians, being men and women of action but needing to abide by the law, are bound to ask the legal limits of what actions they may take in a given case. Ethical limits are generally too fuzzy to serve as a guide to action in today's litigious environment.

Consider as well the relative incentives and penalties for taking a clinical course of action that could be unethical or illegal. Besides high self-esteem—not usually lacking in physicians anyway—and (maybe) the respect of patients and peers, what tangible reward is there for making an ethical decision in a tough case? What serious penalty is likely to follow an unethical, but legal, course of action?

In contrast, imagine trying to defend a physician in today's courts for doing the right thing ethically while knowing it might be illegal. Keep in mind the ethical compromises physicians must make every day while trying to provide good patient care in a cost-contained, resource-limited practice environment. Do not forget the second-guessing by a plaintiff's attorneys and expert witnesses who have had months to analyze a decision that a physician had to make in a matter of minutes.

Of course it is important not to mistake law for ethics and vice versa, but if you are on a hard case and you are not sure what to do, which mistake would you rather make? That is why I will still want to know, "What does the law say?"

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* * *

Dr De Ville Responds

To the Editor: I appreciate Dr Nicholson's thoughtful letter and believe that his comments will find much support.

Given the present state of medicine and law, it is important that physicians know what the law says about relevant aspects of their work; however, an overreliance on "what the law says" tends to taint both clinical decision making and ethical reasoning. For example, a medical

staff gathers to discuss the situation of a profoundly ill and permanently injured neonate. The attending physician (or ethicist, or staff attorney) begins the meeting by writing the federal and state "Baby Doe" regulations on the blackboard. The ensuing discussion has now taken on and is dominated by this legal frame of reference, the unstated assumption often being that this framework is primary and replaces or trumps the "best interest standard." Legal approaches to problems engender habits of mind that are profoundly difficult to overcome.

I would suggest only that ethics committees, medical staff, and individual practitioners defer discussion or consideration of the legal aspects of a case until they have concluded their clinical and ethical deliberations. At that point, if there are relevant legal considerations, the decision maker can face squarely and honestly whatever conflicts arise.

Dr Nicholson reminds us that physicians are "men and women of action" and require guides to practice. Ethical limits, he argues, are too "fuzzy" to serve as such guides; he would much prefer to rely on legal guides. This position appears to assume that legal guides and standards are not fuzzy. From my experience, there is very little that is definitive or clear about medical jurisprudence primarily because medical law, like medical practice, is very much a case-by-case endeavor. More often than not, when I tell medical professionals what "the law says," all I can tell them is maybe. This frustrating level of legal uncertainty is all the more reason to suggest that legal reasoning and concerns should play a highly circumscribed role in ethical deliberations.

Dr Nicholson also argues that legal penalties are more onerous than those imposed for ethical violations. Perhaps. I believe, however, that most physicians are in the profession to do the right thing—to help their patients. They have a personal, moral commitment to their calling. To many practitioners, the greatest penalty of all is to be robbed of one's professional identity by focusing on what one believes the law says instead of what one believes is proper and ethical care. And, these losses are ones against which no one can insure. Dr Nicholson suggests that juries would be much more sympathetic to physicians who follow the dictates of the law than to those who do the right thing. He may be correct, but it is not obvious. It may sometimes be quite difficult to divine the correct or safest legal posture prospectively. Moreover, there is substantial evidence that juries attempt to dispense a form of rough justice, frequently straying from the technical dictates of the law to reward or at least protect those defendants who do the right thing.

Dr Nicholson's comments regarding the relative penalties for illegal and unethical behavior raise another interesting problem. Self interest (in the form of self protection) is a legitimate consideration when choosing among various alternative courses of action. This observation is true in medicine as well as in other areas of life, even though physicians have limited the role of self interest somewhat by pledging to act in the best interest of their patients. But the existence of self interest as a motivating factor in decision making does not alter the essential content of one's ethical duty or of the relevant legal mandates. It merely plays a role in determining how fully physicians will comply with what they see as their ethical and legal duties. Having worked in a medical malpractice defense office, I understand that physicians have a personal need and a professional right to take some protective measures. It is imperative to remember, however, that one's choice of protective measures is itself a vexing ethical problem.

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

Depression, Fatigue, and Memory Loss

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The disheartening emptiness of my early days in practice was vicariously remedied by an occasional night on call that I took for an elderly friend. This physician was literally adored by his patients. I was particularly impressed by how often he remained the physician in charge of three generations of the same family, even long after members of those generations had stopped talking amicably to each other.

One day I was having lunch with my benefactor in a hospital cafeteria when he called out to an approaching physician: "Where have you been all this time? The last time I saw you, you really looked run down. Thank God, now you look great. Tell us what happened to you."

The other physician sat down and, after a round of introductions, told us his story.

"I am well now, but I did not have an easy time. It started several months ago with a vague feeling of fullness in my epigastrium and bouts of really explosive diarrhea. Needless to say, I tried a number of remedies. They were ineffective. My concern and worry escalated. I felt depressed, moody, and irritable. When I developed paresthesia in the fingers I decided to behave like a grown-up and stop this "do-it-yourself" medicine. When my physician told me that all my blood tests were normal, that he found no cause for alarm on an upper gastrointestinal study, and that there was no occult blood in my stools, I felt reassured. He told me that I was depressed, and I could not deny that: he knew I was going through a divorce. It was not surprising that he should conclude that my complaints were psychosomatic.

"After the divorce became final I felt somewhat better, but improvement was very brief. The numbness spread up my legs and began to involve the saddle area. I began to notice a tight feeling in the chest when breathing. I felt short of breath. I lost interest in work and in patients. I also lost my stamina. I had to drag myself in order to function, but I was not anemic. After another battery of tests and a myelogram, I was given a clean bill of health by another friend who attributed my hyperventilation and my other indisputably psychosomatic symptoms to my mother's death.

"Then I came to realize that not only had my mood changed, but also my memory was failing. I could not recall familiar phone numbers or the punch line of a joke I was about to tell. The ominous thought that I could be developing serious brain pathology was frightening, but I literally panicked on the day my ankle went limp. I missed the brake pedal, and I almost killed myself in a crash. Suspecting a brain tumor, the very next morning I flew east to my alma mater.

"Once there, I immediately consulted an old friend of mine who had become a leading internist. He found that I had developed a florid peripheral neuritis. He drew a blood sample right in his office, and it turned out that, for practical purposes, that was all that was needed. Accustomed to examining the blood smear himself, he had immediately noticed my hypersegmented polys.

"Thereafter every study corroborated his presumptive diagnosis of atrophic gastritis with pernicious anemia. And several things I had known about suddenly became explicable: my achylia gastrica, found incidentally many years ago during a physiology exercise; my more recent glossitis that I had blamed on a dentifrice used to clean my dental plate; and the curious ridging and flattening of my nails. How my body had managed to function without gastric acid for so many years and why my pernicious anemia developed so late is certainly a mystery. What is not a mystery is that pernicious anemia starts as a sensory neuropathy which, if recognized and treated, never goes on to the spastic ataxia that characterizes subacute combined degeneration."

Eager to show off my medical knowledge, I asked, "So did your friend start right away giving you vitamin B-12 every day while counting your reticulocytes?"

He smiled and said: "Well, no. He had never seen a peripheral neuritis of nutritional origin as florid as mine. So he convinced me that as a token of gratitude to my alma mater I should donate a piece of a peripheral nerve to their permanent collection of pathology slides. Treatment started after the biopsy was completed."

He then described the dramatic and overpowering feeling of revitalization he experienced within days of starting vitamin B-12 injections and the incredible speed at which he recovered normal mentation and recall capacity. He lamented his mistake of consulting colleagues who had stopped looking at blood smears and who, familiar with his personal plights, could not resist the lure of psychosomatic explanations.

"Oh no!" the elderly family physician interjected, "Your real error was not consulting me in the first place. I give all my patients B-12 shots!"

(Mustacchi P: Depression, fatigue, and memory loss. West J Med 1994; 161:194)

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No reprints available.

The Last Rancher in San Jose

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I read my patient's obituary in the paper: "Tony Torres, rancher, aged 80 years. Survived by nieces Carmen Gonzales and. . . ."

Tony came up from Mexico to California as a young man. Back in the 1930s, San Jose was a farm town, nothing but orchards, canneries, and fruit packing plants. My older patients tell me that back then the air was so clear the Boy Scouts used to semaphore to each other at night using flashlights, blinking words across the valley from Mount Hamilton to the Santa Cruz Mountains. Tony and his brother picked fruit and chopped beets, learned enough English to supervise the labor teams, and saved every cent they could. They worked on a ten-acre ranch owned by an old Italian guy and by the 1940s had saved enough money to buy the place. It sat up in the foothills and overlooked the valley from what would become, a few decades later, the most valuable real estate in the county. His brother eventually married and moved away, but Tony kept the ranch profitable through the 1960s. Then the changes began.

The orchards disappeared. The cash crops became computer chips and housing developments, not apricots and prunes. Tony struggled for years to maintain his ranch and keep his trees alive. He laid irrigation pipes, hired workers to help with the shrinking harvest, and cursed the real estate developers who bought up the land around him. When the canneries all closed down he put up a fruit stand at the top of the dirt road that curled down to his stucco and Spanish tile house.

Tony's neighbors no longer were ranchers, but wealthy executives with enough money to buy the four- and five-bedroom ranch style homes. The newcomers would purchase some of Tony's harvest, but mostly it went to waste. On their way down to Silicon Valley his neighbors smiled wistfully at the old gray-haired Mexican guy who sat on a folding chair in front of the "Fresh Apricots and Prunes" sign; no one could understand why he did not sell the land and cash in—all that valuable real estate going to waste.

The drought killed his trees and everything dried up. Tony began keeping to himself, although his nieces, who were his only relations, would stop by now and then for a visit.

"*Tío* Tony," his niece Carmen would plead, "You ought to sell this place. You could retire and then go relax, not worry about these old trees. The old times are gone. There is no reason to keep up this orchard!"

"No, Carmen, never," he would insist. "I'm not going to live down there." Tony would shove a callused hand out toward the smog hugging the valley. "I won't go live in town. All that noise. They are all crazy, no? *Todos están locos*!"

Carmen and her sister began cleaning their uncle's house once a week. They brought up groceries because he stopped leaving his old ranch. What started them worrying was that he neglected even washing a dish, and he let the mess just pile up, not even keeping himself clean properly. They would come in and find Tony talking to himself, the stovetop burners on and saucepans scorched. Once Carmen discovered him in the toolshed; he was fumbling around with rusted irrigation piping and swearing because he could not find a decent pipe wrench.

"*Tío*, all your trees are dead. There is nothing to bring in from them. *No hay fruta!* Why are you out here?"

After that episode Carmen dragged Tony into the clinic to see a physician. Until our first meeting, Tony had not been to a physician for his entire 79 years.

He was thin and wiry, his bronzed face unshaven and seamed by the years spent out-of-doors. Tufts of gray hair peeked out from underneath a Stetson-style cowboy hat, which he wore with dignity. He had on a blue work shirt and worn Levis, held up by a faded brown leather belt. Tony wore snakeskin cowboy boots with two-inch heels; even with them he was a short man. He spoke to me in the hybrid Spanish-English used by his generation of immigrants.

"*No, Doctor, no tengo nada. Me siento bien.* I don't have anything wrong. I feel fine." He looked at his niece with worried, sideways glances.

I examined him carefully and tested his mental status. He seemed a little undernourished—nothing too serious. Although he had little trouble regaling me with stories about San Jose before the war, he did not know the current year or month.

"Oh, don't worry about those things," he scoffed.

I sent him off to the laboratory and spoke to Carmen.

"Well, he seems all right physically. I am sending off a few simple blood tests, and I will prescribe some vita-

(Hoch DF: The last rancher in San Jose. West J Med 1994; 161:195-196)

From the Division of Primary Care, Department of Medicine, Santa Clara Valley Medical Center, San Jose, California.
Reprint requests to Dana F. Hoch, MD, Chaboya Clinic, 2410 Senter Rd, San Jose, CA 95111.

mins for him. But as you probably know, there is not much I can do about his mind." I sighed with a mixture of profound respect and sadness for the old rancher.

"My uncle's only wish is to stay on his ranch, Doctor. My sister and I will do our best to keep him there." She smiled and shook her head, like a mother trying to understand a misbehaving, temperamental child.

I saw Tony every month; he went downhill quickly. Carmen's sister, a nurse's aide, moved into Tony's spare bedroom. She kept the house safe and Tony clean. My drugs kept him asleep at night and prevented him wandering out to the toolshed alone, where he could have injured himself. Eventually the Stetson he wore so proudly was replaced by a sagging baby blue knit ski cap. Tony's cowboy boots were replaced by house slippers and his Levis by diapers and flannel pajamas. At the end he just refused to eat or drink. He died at home, his nieces at his bedside.

I think about Tony Torres often. I admire my patient's stubborn refusal to sell his ranch, the way he persevered with working it as long as he could. He could have taken the easy road and accepted the new ways and sold his ten acres. He probably would have eventually wound up in a retirement community like most of his contemporaries, watching television and waiting for the next illness. On the other hand, there is something pathetic about how Tony refused to accept the inevitability of change. His ranch became an anachronism and a symbol of his mental and eventual physical deterioration.

In a similar way to my patient's, there are forces at work in my life over which I have little control, forces that are changing my professional and personal life. Decisions made by politicians in Washington and my own hospital administrators have profound effects upon my daily practice. How can I adapt to the new ways, perhaps anticipate and influence them, and yet maintain my integrity and a sense of creativity? Will I, too, near the end, peer sadly out at the world from under a knit cap, with vacant eyes, desperate for reassurance that everything will be fine and just as I remember it?

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

In Memoriam

California Medical Association

ACHKI, CHARLES, Fresno. Died Jun 3, 1994, aged 70. Graduate of University of Istanbul, 1950. Licensed in California in 1957. Dr Achki was a member of the Fresno-Madera Medical Society.

❧

BEATON, COLIN, Los Gatos. Died Jun 8, 1994, aged 96. Graduate of University of Toronto Faculty of Medicine, 1923. Licensed in California in 1937. Dr Beaton was a member of the Santa Clara County Medical Association.

❧

BINGHAM, ROBERT, Desert Hot Springs. Died May 1, 1994, aged 83. Graduate of University of Colorado School of Medicine, Denver, 1938. Licensed in California in 1946. Dr Bingham was a member of the Riverside County Medical Association.

❧

BULLER, WILMER, Bakersfield. Died Jun 20, 1994, aged 78. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1944. Licensed in California in 1945. Dr Buller was a member of the Kern County Medical Society.

❧

COSTELLO, JOHN A., Palm Springs. Died Jun 17, 1994, aged 90. Graduate of University of California, Irvine, California College of Medicine, 1962. Licensed in California in 1975. Dr Costello was a member of the Riverside County Medical Association.

❧

DULLNIG, MICHAEL MAX, Sacramento. Died Jun 1, 1994, aged 37. Graduate of Southwestern Medical School, Dallas, Texas, 1982. Licensed in California in 1983. Dr Dullnig was a member of the Sacramento-El Dorado Medical Society.

❧

FAHEY, NORBERT J., Sacramento. Died May 22, 1994, aged 69. Graduate of Marquette University School of Medicine, Milwaukee, Wisconsin, 1950. Licensed in California in 1953. Dr Fahey was a member of the Sacramento-El Dorado Medical Society.

❧

FISCHER, FREDERICK N., Sacramento. Died Jun 18, 1994, aged 69. Graduate of University of Zurich, 1954. Licensed in California in 1957. Dr Fischer was a member of the Sacramento-El Dorado Medical Society.

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GREEN, ALBERT J., Walnut Creek. Died Jun 23, 1994, aged 57. Graduate of Meharry Medical College, Nashville, Tennessee, 1963. Licensed in California in 1967. Dr Green was a member of the Alameda-Contra Costa Medical Association.

IGER, MORTIMER, Bakersfield. Died Jun 16, 1994, aged 79. Graduate of New York University School of Medicine, New York, 1939. Licensed in California in 1953. Dr Iger was a member of the Kern County Medical Society.

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ISMAEL, ISMIL, San Jose. Died Jul 3, 1994, aged 50. Graduate of State University of New York, Buffalo, 1972. Licensed in California in 1976. Dr Ismael was a member of the Santa Clara County Medical Association.

❧

JENKINS, HERBERT W., Sacramento. Died May 28, 1994, aged 80. Graduate of Stanford University School of Medicine, Stanford, California, 1940. Licensed in California in 1940. Dr Jenkins was a member of the Sacramento-El Dorado Medical Society.

❧

KOTNER, IRVIN A., San Bernardino. Died May 26, 1994, aged 77. Graduate of Washington University School of Medicine, St Louis, Missouri, 1942. Licensed in California in 1952. Dr Kotner was a member of the San Bernardino County Medical Society.

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LEVIN, EDWARD A., San Francisco. Died Jun 9, 1994, aged 88. Graduate of University of California, San Francisco, 1932. Licensed in California in 1932. Dr Levin was a member of the San Francisco Medical Society.

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MILLER, MILTON MERRIT, Napa. Died Jun 29, 1994, aged 85. Graduate of Loma Linda University, Loma Linda, California, 1947. Licensed in California in 1947. Dr Miller was a member of the Napa County Medical Society.

❧

NADJMABADI, FEREYDOUN, Walnut Creek. Died May 27, 1994, aged 55. Graduate of University of Tehran, 1965. Licensed in California in 1973. Dr Nadjmabadi was a member of the Alameda-Contra Costa Medical Association.

❧

ODLAND, THEODORE M., Fresno. Died Jun 9, 1994, aged 70. Graduate of Oregon School of Medicine, Portland, 1953. Licensed in California in 1956. Dr Odland was a member of the Fresno-Madera Medical Society.

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PULLEY, HAMLET C., Berkeley. Died Mar 21, 1994, aged 91. Graduate of St Louis University School of Medicine, St Louis, Missouri, 1937. Licensed in California in 1938. Dr Pulley was a member of the Alameda-Contra Costa Medical Association.

SCHULTE, THOMAS L., San Francisco. Died May 30, 1994, aged 84. Graduate of Stanford University, 1936. Licensed in California in 1936. Dr Schulte was a member of the San Francisco Medical Society.

❧

SHANNON, CHARLES R., Sacramento. Died Apr 25, 1994, aged 73. Graduate of Stanford University School of Medicine, 1952. Licensed in California in 1952. Dr Shannon was a member of the Sacramento-El Dorado Medical Society.

❧

SIMMANG, ARTHUR V., Fresno. Died May 26, 1994, aged 80. Graduate of University of Texas Medical Branch, Galveston, 1938. Licensed in California in 1943. Dr Simmang was a member of the Madera Medical Society.

❧

THOMPSON, ROBERT K., Saratoga. Died Jun 19, 1994, aged 61. Graduate of University of Manitoba Faculty of Medicine, Winnipeg. Licensed in California in 1963. Dr Thompson was a member of the Santa Clara County Medical Association.

❧

THORPE, PATRICK HILTON, Dixon. Died Jun 22, 1994, aged 44. Graduate of University of Louisville School of Medicine, Louisville, Kentucky, 1977. Licensed in California in 1978. Dr Thorpe was a member of the Humboldt-Del Norte Medical Society.

❧

WHALEN, WILLIAM J., Sacramento. Died May 29, 1994, aged 65. Graduate of University of Illinois College of Medicine, Chicago, 1954. Licensed in California in 1957. Dr Whalen was a member of the Sacramento-El Dorado Medical Society.

❧

WOODARD, MARGOT H., San Francisco. Died May 5, 1994, aged 66. Graduate of University of New Mexico School of Medicine, Albuquerque, 1968. Licensed in California in 1971. Dr Woodard was a member of the San Francisco Medical Society.

Denver Medical Society

MILLER, EDWARD SIDNEY. Died Jun 23, 1994, aged 77. Graduate of Harvard Medical School, Boston, Massachusetts, 1940. Licensed in Colorado in 1948.

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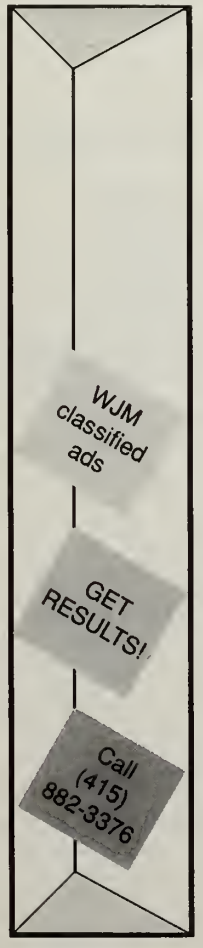

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FAMILY PRACTICE POSITION AVAILABLE NOW. Progressive three-physician, four-physician assistant group needs full-time Board Certified Family Practitioner. Immediate availability. After one-year trial period, partnership available with minimal investment. Competitive salary and benefits. Contact Sue Deegan PO Box 20700, San Jose, CA 95160. (408) 997-9155.

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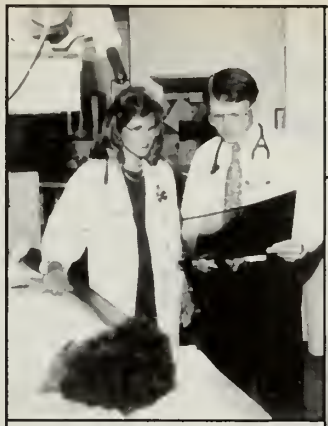
SOUTHERN CALIFORNIA. Rural non-profit health clinic needs a General Practitioner who desires: direct primary health care, participation in chart review and quality assurance, clinic hours to only 7:00 pm, minimum hospital admissions, hospital on call two weekends per month, excellent benefits, malpractice 100% paid. Please send CV to: Clinicas de Salud del Pueblo, Inc., Personnel Office, 1116 "K" St, Brawley, CA 92227.

OREGON. FAMILY PRACTICE clinician teachers needed for Oregon Health Sciences University Department of Family Medicine. We seek clinician teachers for new neighborhood practices. Duties are chiefly patient care plus some resident and student teaching. Obstetrics and hospital care of patients desired. Send CV and three references to L.J. Fagnan, MD, Dept of Family Medicine, OHSU, Mail Code FP Portland, OR 97201-3098. AA/EO Employer.

(Continued on Page 202)

WJM ADS GET RESULTS

R&Rx



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Arizona: CIGNA HealthCare of AZ, Physician Recruitment, 11001 N. Black Canyon Hwy., Suite 401-49, Phoenix, AZ 85029, (800) 252-2471. EOE.

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(Continued from Page 201)

PHYSICIANS WANTED

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Northwest Permanente, P.C., a professional group of physicians providing medical services to 380,000 members of Kaiser Permanente in Oregon and SW Washington, has full-time and part-time opportunities in general family practice or urgent care for BC/BE Family Physicians and Internists in the Portland/Vancouver and Salem, OR areas and Longview, WA. In Salem, opportunities exist for Family Physicians or Internists with a special interest or expertise in geriatrics.

Our program offers a professionally stimulating environment, a quality lifestyle in the Pacific Northwest, signing bonus and a competitive salary/benefits package. **Forward inquiry and C.V. to: W. J. Weiland, M.D., Regional Medical Director, NORTHWEST PERMANENTE, P.C., 2701 N.W. Vaughn St., #300, Portland, OR 97210-5398. EOE.**

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Please send CV to:
Joyce Marks–President
Marks Medical Placements
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Or Call: (310) 556-2126, FAX (310) 556-1604

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REWARDING OPPORTUNITY to practice the full range of Family Medicine (with Obstetrical option if desired) in a long-standing community health center. BC/BE Family Practitioners needed to join existing staff composed of Family Physicians, Internists, and Pediatricians on the Waianae Coast. Academic positions also available. Full benefits package and competitive salary. If interested, call or send CV to Pua Kalawa, Waianae Coast Comprehensive Health Center, 86-260 Farrington Highway, Waianae, HI 96792; (808) 696-7081.

OB/GYN for lucrative practice in the Central Valley of California near San Francisco, Lake Tahoe, and Yosemite. Please call Rebecca for details, (800) 783-4184.

PHYSICIANS WANTED

california pediatricians

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Call Paul DeVivo or Lynn Adamson (800) 538-4766 days, evenings, or weekends. Or FAX your CV to (510) 233-4019. Levison Associates, 6039 Park Ave, Richmond, CA 94805.

PACIFIC NORTHWEST AND ROCKY MOUNTAIN/ SOUTHWEST LOCATIONS. Locum tenens assignments in Emergency Medicine, Primary Care, and Radiology. Urgent need for locum tenens. Benefits include malpractice, lodging, and transportation. Assignments vary in duration. Permanent placement also available. Call or write Lorie or Susan, Interim Physicians, 4155 E Jewell, #1018, Denver, CO 80222; (800) 669-0718.

BC/BE FAMILY PRACTITIONER with interest in OB and a commitment to caring for the underserved needed to join clinics in Grandview and Walla Walla, Washington, and Hermiston, Oregon. All clinics located in rural settings with abundant recreational activities. Competitive salary, Public Health Service loan repayment slots, and excellent benefit package including paid malpractice. Contact Mayling Chin, Recruiting Specialist, or Ann Garza, Director of Personnel at Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948, or (509) 865-5898.

CALIFORNIA, ACADEMIC, MULTISPECIALTY group practice seeks Family Practitioners, Internists, and Pediatricians for Primary Care practice opportunities. These physicians will qualify for faculty appointment in the School of Medicine. They will admit patients to the school's three teaching hospitals. They will refer specialty cases to faculty colleagues. Competitive salaries are being offered with potential for incentive bonus. A comprehensive benefit package is provided. Respond to Loran Hauck, MD, Medical Director, Loma Linda Faculty Medical Group, 11370 Anderson St, Ste 3000, Loma Linda, CA 92354; (909) 799-3315.

CALIFORNIA. MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Medicine or Family Practice specialists preferred. Contact Rob Colyn, VP of Personnel, Doctors on Duty Medical Clinics, 19000 Portola Dr, Ste 100, Salinas, CA 93908; (408) 455-2424.

ENJOY THE GREAT SOUTHWEST. Thomas-Davis Medical Centers, one of Arizona's fastest growing multispecialty groups is seeking BC/BE Internal Medicine, Family Practice, OB/GYN, and Hematology/Oncology Physicians. 200 physicians strong, TDMC has provided health care services in Arizona for more than 75 years. For more information regarding this practice opportunity, contact William Trainor, TDMC, 6135 N 7th St, Phoenix, AZ 85014, or call (800) 539-2529, or FAX CV to (602) 530-6255.

CALIFORNIA. Ambulatory Care/Family Practice–CEP is a partnership of Ambulatory Care and Emergency Medicine specialists. We currently staff nine free-standing clinics in northern, central, and southern California, and have upcoming openings for physicians specializing in Family Practice. We offer shared ownership, excellent compensation, health, and disability insurance, retirement program, and many other benefits. For more information, send CV or call John Gravette, CEP, 2101 Webster St, Ste 1050, Oakland, CA 94612; (800) 842-2619.

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OREGON. Medical Director needed for Oregon Health Sciences University Department of Family Medicine. Duties are to provide patient care and resident and student teaching at the Family Practice patient care clinic. Obstetrics and hospital care of patients desired. Send CV and three references to L.J. Fagnan, MD, Dept of Family Medicine, OHSU, Mail Code FP, Portland OR 97201-3098. AA/EO Employer.

SAN FRANCISCO BAY AREA. BC/BE PRIMARY CARE INTERNIST or Family Practitioner to join Marin Community Clinic, serving a low income, 40% Hispanic population. 80% clinical, 20% administrative duties as Medical Director. On the Marin General Hospital campus, 20 minutes from San Francisco. CV to Nance Rosencranz, MCC, PO Box 760, Larkspur, CA 94977, or FAX (415) 461-7334.

FAMILY PRACTITIONERS. Immediate locum tenens and permanent assignments for Family Practitioners who do Obstetrics. Ongoing needs in numerous states. We compensate. We insure.. Call Frank Canaday today toll-free at (800) 226-6347 for details. "HKA...Placing tomorrow's healthcare needs today."

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OREGON/WASHINGTON. BC FAMILY PRACTITIONER to join expanding single specialty group. Multiple clinic sites near Portland and Seattle. Income guarantee, excellent benefits, partnership. Enjoy the Northwest—hiking, boating, skiing, and abundant cultural activities. Practice with congenial colleagues who balance quality medicine with quality lifestyle. Call Jan, (800) 789-1190 or (206) 389-9191.

CALIFORNIA. Ambulatory Care/Family Practice–CEP is a partnership of Ambulatory Care and Emergency Medicine specialists. We currently staff nine free-standing clinics in northern, central, and southern California, and have upcoming openings for physicians specializing in Family Practice. We offer shared ownership, excellent compensation, health, and disability insurance, retirement program, and many other benefits. For more information, send CV or call John Gravette, CEP, 2101 Webster St, Ste 1050, Oakland, CA 94612; (800) 842-2619.

PACIFIC NORTHWEST. Placement specialists serving northern California, Oregon, Washington. City or rural, group or solo. Internal Medicine, Family Practice, OB/GYN, General Surgery, Pediatrics, and all other specialties. Barbara Stoefen, President, The O'Kane Group, 25 NW Minnesota Ave, Ste 7, Bend, OR 97701; (800) 451-0700, FAX (503) 389-5134.

SACRAMENTO. BC/BE PHYSICIAN for busy urgent care center. Excellent package with early partnership. Send RV to Number 298, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

THINKING OF PLACING AN AD IN OUR NEXT ISSUE? The deadline for the October issue is September 1st. Don't delay. Call (415) 882-3376 to place your classified ad today.

(Continued on Page 203)

(Continued from Page 202)

PHYSICIANS WANTED

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EXCELLENT OPPORTUNITY. Large multispecialty group with an expanding Division of Occupational Medicine has an immediate opening for a qualified, energetic physician. We are seeking a career-minded physician with superb clinical and communication skills. Experience with managed care, computers, and teaching is desirable.

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(408) 730-4309

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Leading medical providers in Arizona, Nevada, Utah, Colorado, and New Mexico have asked us to find the best available BC/BE physicians in the specialties of Orthopedic Surgery, Internal Medicine, Family Practice, Pediatrics, Urgent Care, OB/GYN, Psychiatry, Hematology/Oncology, Radiology, Occupational Medicine, ENT, MED/PED, Cardiology, Nephrology, and Pulmonology. Top benefits, profit sharing, guarantee first two years, plus incentive pay, early shareholder. Please call CPR Tucson, (800) 658-9166, FAX (602) 322-2676, or in Phoenix, (800) 657-0354, FAX (602) 433-9548.

COME TO THE LAND OF ENCHANTMENT. Sunny New Mexico seeking senior physician for 300-bed state-operated facility for people with developmental disabilities. Seeking individual who is looking for a challenge and personal growth, able to provide primary care to adolescents and adults with developmental disabilities, willing to work on a multidisciplinary team, and willing to provide education to University of New Mexico trainees. Potential for academic appointment. Minimum qualifications: graduation from an accredited medical school, completion of an approved internship and licensure by the New Mexico Board of Medical Examiners. For information contact Javier Aceves, MD at (505) 841-5226.

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- concentrated audience in 10 western states
- affordable ad rates
- friendly staff

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(415) 882-3376

PHYSICIANS

San Mateo County, located 30 miles south of San Francisco, is currently seeking the following Physicians for our Health Services Department:

- **FAMILY PRACTITIONER or PRIMARY CARE INTERNIST**
- **PEDIATRICIAN**

We're looking for energetic, enthusiastic individuals to establish a new clinic delivering comprehensive primary care to an underserved population. Bilingual skills in English/Spanish highly preferred. Outpatient care only; call not necessary. For consideration, please contact Maren Pedersen, M.D. at (415) 573-3436 or Sue Ferren at (415) 573-2367.

- **STAFF PHYSICIAN**

We're looking for an enthusiastic staff physician to act as an active member of the medical staff at our growing long-term care facility. You'll handle an interesting and active practice consisting of subacute, post-surgical, AIDS and post-stroke care. To qualify, you must be a board certified family practitioner or internist. Experience in rehab, AIDS, med-psych and long-term care preferred. For consideration, contact Harrison Gill, M.D. at (415) 312-5298 or Sue Ferren at (415) 573-2367.

We offer a competitive salary and outstanding benefits package and are an equal opportunity employer.

SAN MATEO COUNTY

PHYSICIANS WANTED

CALIFORNIA. EXCELLENT OPPORTUNITY available in 1994 to early 1995 for a BC/BE oncologist-hematologist to join a busy, two-person, subspecialty practice in San Francisco bay area. Modern facilities available to deliver high quality, outpatient-based, comprehensive cancer care. Protocol participation available through SWOG-NSABP. Extremely competitive salary and benefit package leading to early partnership. Please send CV to Number 297, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NORTHERN CALIFORNIA RECREATION AREA. Multispecialty group has immediate opening for a Family Practice physician. Clinical activities involve full range of Family Practice outpatient and inpatient practice. Beautiful northern California location offers abundant recreational opportunities as well as small town living. Competitive salary and comprehensive benefit package. Please send CV to 10978 Donner Pass Rd, Truckee, CA 96161.

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- INTERNAL MEDICINE
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BECKER PHYSICIAN PLACEMENT
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(Continued on Page 204)

(Continued from Page 203)

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The California Department of Corrections has positions available in one of our newer prison complexes in the **Wasco State Prison Reception Center** near Bakersfield and San Luis Obispo, with easy access to the coast and mountains, and affordable housing in open country for great family living. We offer competitive salary and excellent benefits, and our new safety retirement package. For more information on the positions at Wasco, call:

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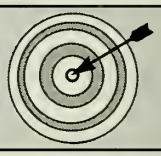

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(Continued on Page 205)

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SAN JOSE MEDICAL GROUP, INC

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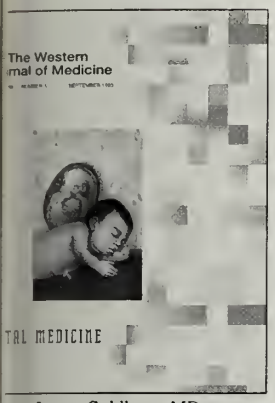
THE WESTERN JOURNAL OF MEDICINE

FETAL MEDICINE

SEPTEMBER 1993



James Goldberg, MD
Special Issue Editor, 1993

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- CARDIAC ULTRASOUND IN STRUCTURAL ABNORMALITIES AND ARRHYTHMIAS—RECOGNITION AND TREATMENT
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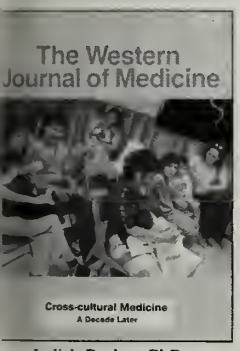

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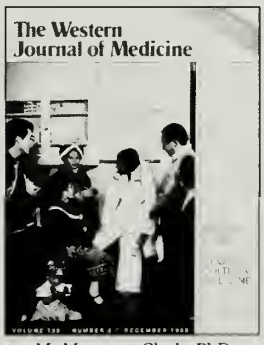

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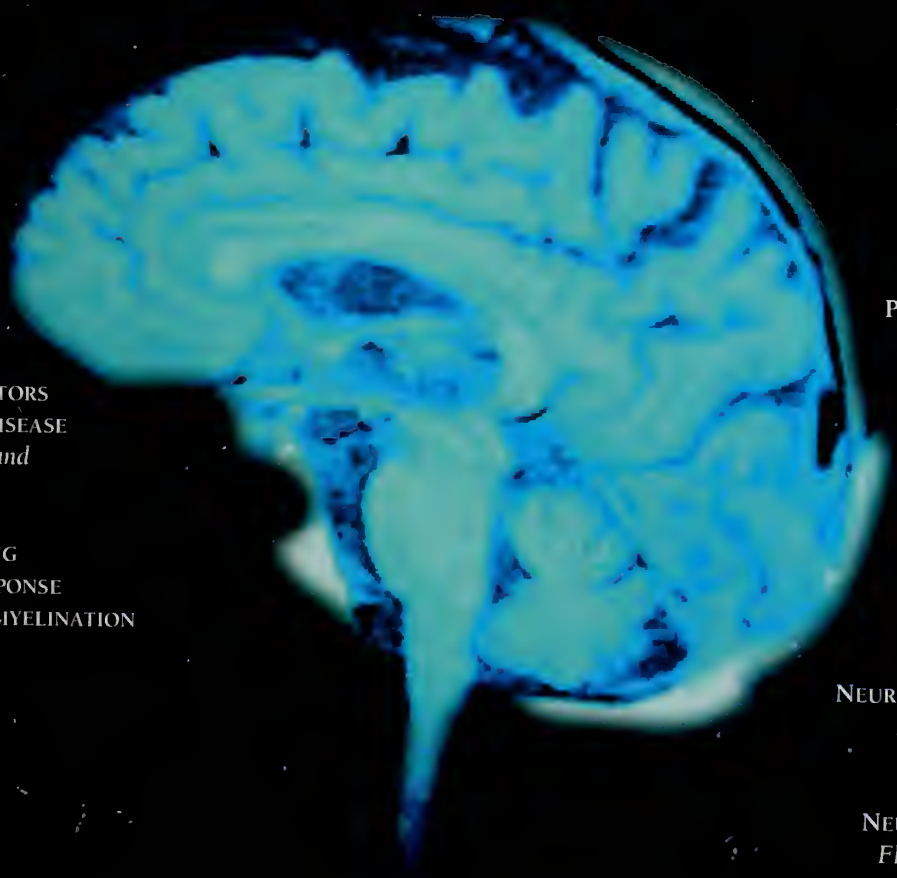

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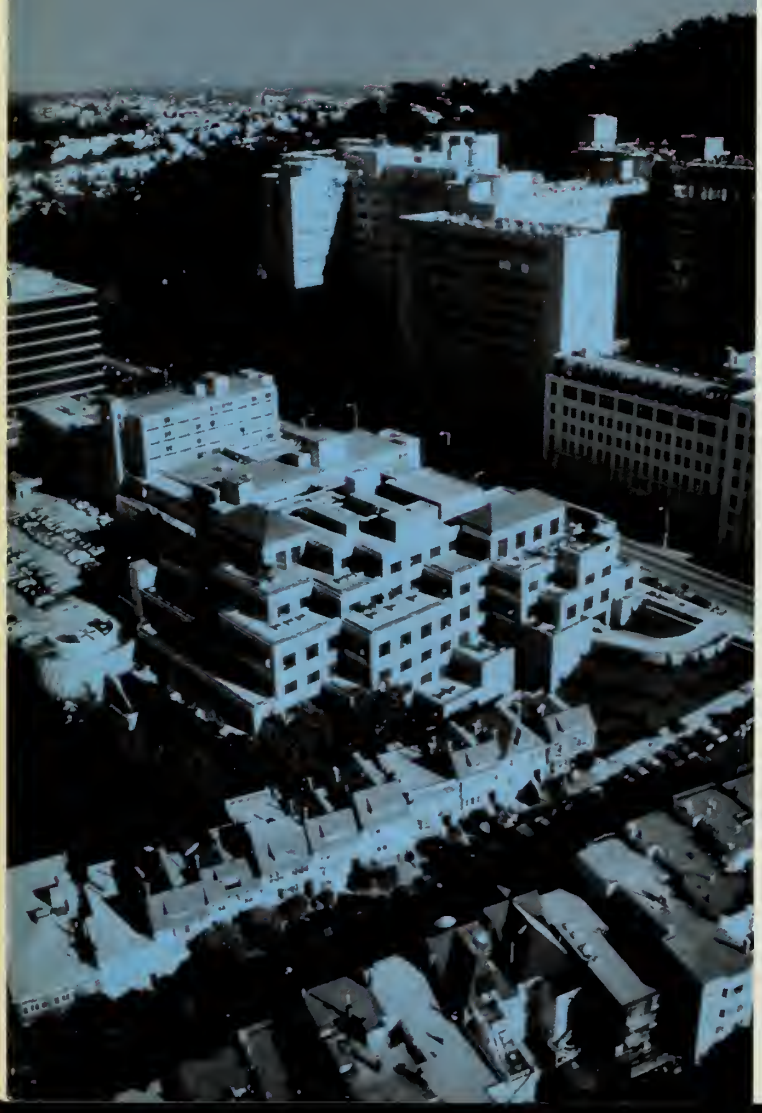

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USC Center For Colorectal Diseases

A CASE STUDY

A 37-year-old male presented with a 17 year history of ulcerative colitis. On rectal exam, a 2 cm. polyp on a stalk was noted and removed. It contained an invasive carcinoma. Surgical judgments and alternatives for the management of this problem are complex.

Current understanding on the margins of resection, use of adjuvant therapy, and the technical issues of continence preservation, interplay in this complex case. Recognition of the appropriate use of nerve sparing rectal dissection with wide lymphadenectomy allowed for an adequate cancer procedure while preserving the sphincter mechanism. A compliant and capacious pouch was created and intestinal continuity was restored.

The patient has recovered, retained his sexual potency and maintained fecal continence with five bowel movements a day. He is fully active and continues long distance running as a hobby.

The USC Center for Colorectal Diseases is a university-based private practice that offers the full range of advanced diagnostic and treatment alternatives for patients with colorectal disease and fecal incontinence. Offering advanced expertise in a university setting, the Center provides primary *and* tertiary management of colorectal disease, including inflammatory bowel disease, ulcerative colitis and Crohn's disease. It conducts sophisticated physiological tests to evaluate anorectal physiology in patients who have difficulty with fecal incontinence.

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Innovative Surgical Alternatives

The Center's specialists have expertise in the surgical alternatives to ileostomy and colostomy, including:

- Koch Pouch: This continent intestinal reservoir allows patients to store waste and control its discharge after coloproctectomy, thus eliminating the need for an external appliance.
- Ileal Pouch-Anal Anastomosis: In this procedure, surgeons create a pouch out of the terminal ilium and sew it to the anal muscles, and perform a temporary ileostomy. Six to eight weeks later, they close the ileostomy, and patients can defecate normally.
- Laparoscopically Assisted Colectomy: Surgeons can now effectively remove segments of the colon through this minimally invasive technique.

The Center's comprehensive services include:

- Colonoscopy
- Management of recurrent colorectal cancer
- Anorectal physiologic studies
- Evaluation of continence disorders
- Continence preserving and restoring surgical procedures
- Post-operative pain management, rehabilitation and education
- Research activities including the physiology of continence and surgical techniques
- Educational activities to support physicians in the development of current surgical techniques

Center surgeons perform all major surgeries at USC University Hospital or USC/Norris Cancer Center. Both facilities provide the latest in technology, patient care and dedicated colorectal trained nurses.

Physician Support and Education

As an academically based program, the Center is dedicated to providing continuing education and support for physicians practicing in the community setting. Physicians are encouraged to contact USC PACE for patient consultation or program information.

About the Director

Robert W. Beart, Jr., M.D., *Professor of Surgery at the USC School of Medicine, serves as Director of the USC Center for Colorectal Diseases. He is a world-renowned specialist in colon and rectal surgery, with extensive experience in performing and refining surgical alternatives to ileostomy and colostomy and laparoscopic colon resection.*

Dr. Beart received his medical degree from Harvard Medical School, and completed his internship and residencies at the University of Colorado Medical Center in Denver. He did a transplant fellowship (liver and kidney) at the University of Colorado, and a colon and rectal fellowship at the Mayo Clinic Rochester. For more than a decade, he served as Chairman, Colon and Rectal Surgery at the Mayo Clinic Rochester, and was named the Caywood Professor of Surgery. At the Mayo Clinic Scottsdale (Arizona), he was Chairman, Department of General Surgery. He joined USC University Hospital in 1992.

Dr. Beart, a member of numerous professional organizations, is the immediate Past President of the American Society of Colon and Rectal Surgeons. He is widely published in peer review journals, is the editor of Diseases of the Colon & Rectum, *and is a much sought after lecturer.*

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Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of YOCON® 1/12 gr. 5.4mg in bottles of 100's NDC 53159-001-01, 1000's NDC 53159-001-10 and Blister-Paks of 30's NDC 53159-001-30

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 7-8—**Clinical Assessment in Today's World of Medicine for Nurses.** Mayo Clinic-Scottsdale at Ashton B. Taylor Auditorium, Scottsdale. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

October 8—**Audiology Videoconference.** Mayo Clinic-Scottsdale. Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

October 14-15—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Doubletree Hotel, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

October 21-22—**Parkinson's Disease and Movement Disorders for the Practitioner.** Mayo Clinic-Scottsdale at Ritz-Carlton Hotel, Phoenix. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

October 28-30—**Arrthymias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Camelback Inn, Scottsdale. Fri-Sun. Contact: Karen DeBont, (800) 421-3756.

November 3-6—**24th Annual Meeting: Musculoskeletal & MRI.** Maricopa Medical Center, Department of Radiology, at Camelback Inn, Scottsdale. Thurs-Sat. Contact: (602) 267-5366.

November 4-5—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

November 4-5—**Hematology and Oncology for Primary Care Physicians.** Mayo Clinic-Scottsdale at the Orange Tree Golf Resort, Scottsdale. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

November 7-11—**The Physician Management Seminar Series: Seminar I.** American College of Physician Executives at the Scottsdale Plaza Resort, Scottsdale. Mon-Fri. Contact: (800) 562-8088.

November 7-11—**The Physician Management Seminar Series: Seminar II.** American College of Physician Executives at the Scottsdale Plaza Resort, Scottsdale. Mon-Fri. Contact: (800) 562-8088.

November 10-12—**7th Annual Techniques in Gynecologic Surgery.** Mayo Clinic-Scottsdale at Marriott's Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

November 14-16—**Hand and Wrist Injuries in the Athlete.** American Society for Surgery of the Hand at Scottsdale. Mon-Wed. Contact: (303) 771-9236.

November 17-19—**Pediatric Orthopaedics: A Comprehensive Course.** American Academy of Orthopaedic Surgeons at The Pointe Hilton Resort at Squaw Peak, Phoenix. Thurs-Sat. Contact: AAOS, (708) 823-7186.

December 2-3—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

December 2-4—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Hyatt Regency, Scottsdale. Fri-Sun. Contact: Karen DeBont, (800) 421-3756.

January 12-13—**2nd Annual Current Topics in Critical Care Medicine.** Mayo Clinic-Scottsdale at the Ritz-Carlton Hotel, Phoenix. Thurs-Fri. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 14-15—**5th Annual Current Topics in Anesthesiology.** Mayo Clinic-Scottsdale at the Ritz-Carlton Hotel, Phoenix. Sat-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 20-22—**Electromyography in Clinical Practice.** Mayo Clinic-Scottsdale. Fri-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 24-26—**1995 Scientific Assembly—American Academy of Family Practice.** The Pointe Hilton at Tapatio Cliffs, Phoenix. Fri-Sun. Contact: American Academy of Family Practice, Arizona Chapter, (602) 249-2021.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

November 11-13—**Anesthesiology Update: 1994.** UCD at Monterey Plaza, Monterey. Fri-Sun. 14 hrs. $325. Contact: UCD.

November 18-19—**4th Annual Pain Conference.** UCD at Inn at Napa Valley. Fri-Sat. 11 hrs. $300. Contact: UCD.

January 4-7—**Anesthesia Update.** UCSD at Hotel del Coronado, San Diego. Mon-Sat. 21 hrs. $350. Contact: UCSD.

February 3-5—**33rd Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: David Steward, MD, Director, PO Box 54700, Los Angeles 90054. (213) 669-2262.

CARDIOLOGY

October 7-9—**Coronary Heart Disease.** Medical Education Resources at Desert Inn, Las Vegas. Fri-Sun. 11 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528.

October 13-15—**Cardiology Update: 1994.** UCSF at Carmel Valley Resort, Carmel. Thurs-Sat. 18 hrs. Contact: UCSF.

October 27-30—**East Visits West: Coronary Interventions 1994.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sun. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, 403C, La Jolla 92037. (619) 554-8556.

November 18-20—**Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. 11 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

December 9-11—**12th Annual Advances in Heart Disease.** American College of Cardiology at San Francisco. Fri-Sun. 16.5 hrs. Contact: ACC, 911 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

DERMATOLOGY

October 15-16—**The Skin From A to Z.** UCSF. Sat-Sun. Contact: UCSF.

November 11-13—**5th Annual Cutaneous Malignancies: 1994 Skin Cancer Update.** Scripps Clinic and Research Foundation at Schaetzel Center for Health Education, La Jolla. Fri-Sun. 16 hrs. Contact: Scripps, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

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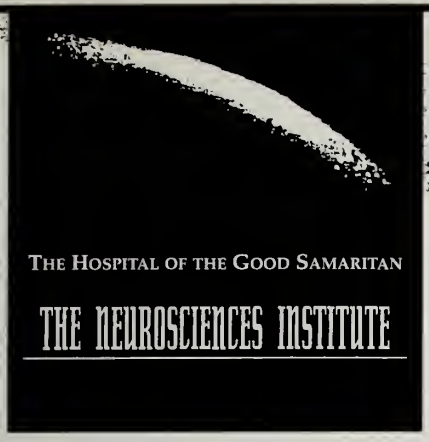

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QD STAYING POWER

Positron emission tomography (PET) image of ^{11}C-triamcinolone acetonide following intranasal administration of Nasacort[1]

ONCE DAILY

Nasacort®

(triamcinolone acetonide) Nasal Inhaler

Provides comfortable, prompt relief of allergic rhinitis and effective QD dosing

- *Nasacort remains in the nasal mucosa with no measurable effect on HPA function [1-3]**

  Duration of acquisition of the PET image was approximately 55 minutes due to ^{11}C decay ($t\,1/2$ of 20 minutes).[1] (n=2)

- *Nasacort provides prompt relief for many patients — symptom reduction may occur as soon as 24 hours after starting therapy [4]*
- *Nasacort provides effective QD dosing — 2 puffs/nostril/day effectively controls symptoms in most patients; however, QD dosing can be increased to 4 puffs/nostril/day when necessary*

Please see brief summary of prescribing information on adjacent page.

** In doses up to 440 mcg/day.[3]*

Nasacort...Once Is Enough

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Nasacort® Nasal Inhaler
(triamcinolone acetonide)

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Shake Well Before Using

BRIEF SUMMARY

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

The use of Nasacort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Nasacort Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

PRECAUTIONS

General: In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local therapy and discontinuance of treatment with Nasacort Nasal Inhaler.

Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. Nasacort at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see CLINICAL TRIALS section).

Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent, tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances.

When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasacort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients being treated with Nasacort Nasal Inhaler should receive the following information and instructions.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Patients should use Nasacort Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations.

Carcinogenesis, Mutagenesis: Animal studies of triamcinolone acetonide to test its carcinogenic potential are underway.

Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m^2/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m^2/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m^2/day or 110 mcg/m^2/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery. Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5 - 15.0 mcg/kg/day or 20 - 110 mcg/m^2/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m^2/day and 7.0 mcg/m^2/day).

Pregnancy: Pregnancy Category C. Like other corticoids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m^2/day in the rat and 320, 640 and 1280 mcg/m^2/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m^2/day). The doses of 0.02, 0.04, 0.08, and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51, and 318.7 times the minimum recommended dose of 110 mcg of Nasacort per day and 3.2, 6.4, 12.7, and 80 times the maximum recommended dose of 440 mcg of Nasacort per day based on a patient body weight of 70 kg. Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Nasacort Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in children below the age of 12. Oral corticoids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS: In controlled and uncontrolled studies, 1257 patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed Nasacort canister. These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days).

The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received Nasacort. Nasal irritation was reported by 2.8% of the patients receiving Nasacort. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received Nasacort and included: dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects.

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).

OVERDOSAGE: Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects if the nasal application of the 15 mg of triamcinolone acetonide was administered all at once.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Please see product circular for full prescribing information.

REFERENCES:

1. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc. **2.** Ziemniak JA: Pharmacokinetics of intranasal triamcinolone acetonide. *J Respir Dis* 1991;12 (3, Suppl):S41-S42. **3.** Feiss G, Morris R, Rom D, et al: A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function. *J Allergy Clin Immunol* 1992;89:1151-1156. **4.** Findlay S, Huber F, Garcia J, et al: Efficacy of once-a-day intranasal administration of triamcinolone acetonide in patients with seasonal allergic rhinitis. *Ann Allergy* 1992;68(3):228-232.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 214)

EMERGENCY MEDICINE

October 14-16—**Advances in Emergency Medicine.** Continuing Medical Associates at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 17-21—**Emergency Medicine Symposium.** UCSD at San Diego Hilton. Mon-Fri. 17 hrs. $475. Contact: UCSD.

November 7-11—**Emergency Medicine Symposium.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

December 4-9—**15th Annual Conference: Current Concepts in Emergency Care.** American College of Emergency Physicians at Maui Intercontinental Resort, Hawaii. Sun-Fri. 20 hrs. Contact: Kailani World Travel, 4192 Meridian Ave, Box 9751, Bellingham, WA 98227. (800) 544-9269 or (206) 671-1800.

December 12-16—**Emergency Medicine Symposium.** UCSD at Basic Science Building. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 16-20—**Emergency Medicine Symposium.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 24-29—**California Trauma Conference.** UCSD at Hyatt Regency, San Diego. Tues-Sun. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

November 5—**Neurology for Primary Care.** UCD at Cancer Center Auditorium. Sacramento. Sat. 7 hrs. $95. Contact: UCD.

November 5—**What to Do About Hypertension in 1995.** American Society of Hypertension at Hotel Nikko, Beverly Hills. Sat. 4 hrs. Contact: ASH, 515 Madison Ave, #1212, New York, NY 10022. (212) 644-0650.

December 9-11—**Neurology for the Non-Neurologist.** American College of Emergency Physicians at Desert Inn, Las Vegas, Nevada. Fri-Sun. 12 hrs. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

December 24-29—**Advances in Medicine '94.** American Academy of Family Physicians and Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Lahaina, Maui, Hawaii. Sat-Thurs. 16 hrs. Contact: Joe Harrison, MD, PO Box 10185, Lahaina, HI 96761. (808) 878-6757.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs, (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

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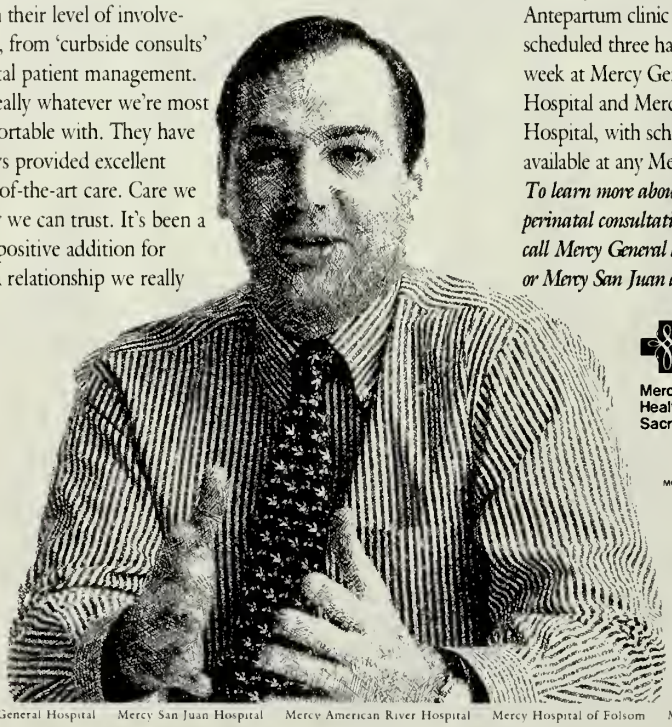
To learn more about Mercy's perinatal consultation services call Mercy General at 453-4140 or Mercy San Juan at 537-5339.



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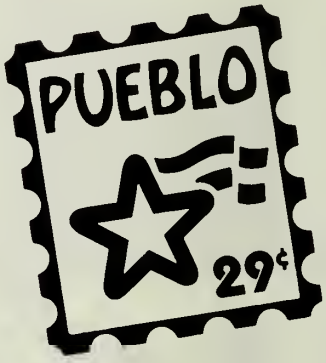

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★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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November 8-11, 1994 • The Hilton, Walt Disney World Village

2nd Annual How to Create Antibiotic Management Programs that are Clinically Sound (Quality Assurance) and Cost-Effective
November 21-23, 1994 • The Contemporary Resort, Walt Disney World

2nd Annual Update on Congenital Heart Disease
January 26-28, 1995 • Disney Contemporary Hotel

18th Annual Advanced Ultrasound Seminar: OB/GYN
February 2-4, 1995 • Disney Yacht and Beach Club

16th Annual International Gastroenterology Conference
February 8-11, 1995 • The Hilton, Walt Disney World Village

6th Annual Emergency Medicine for the Critically Ill and Injured
February 23-26, 1995 • Disney Yacht and Beach Club

17th Annual Management of the Tiny Baby Conference
February 16-18, 1995 • Disney Contemporary Hotel
(for more information call 407-841-5218)

5th Annual Breast Imaging Conference
March 9-11, 1995 • Yacht and Beach Club Resorts, Walt Disney World Village

19th Annual Internal Medicine Series
March 27-31, 1995 • The Hilton, Walt Disney World Village

19th Annual Infectious Disease & Antibiotic Therapy Conference
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15th Annual Critical Care Medicine Conference
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(P L E A S E P O S T)

CONTINUING MEDICAL EDUCATION

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January 20-22—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 2-4—**Neurology for the Non-Neurologists.** UCSD at Doubletree Hotel, San Diego. Thurs-Sat. Contact: UCSD.

February 14-19—**The Practicing Physician's Approach to the Difficult Headache Patient.** Dannemiller Memorial Educational Foundation at Marriott's Rancho Las Palmas Resort and Country Club, Rancho Mirage. Tues-Sun. Contact: Diamond Headache Clinic, 5252 N Western Ave, Chicago, IL 60625. (312) 907-6226.

February 17-19—**Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

GERIATRICS

October 7-8—**Coming of Age: Geriatrics for the Primary Care Provider—Part II.** UCD at Sacramento Inn. Fri-Sat. 13 hrs. $235. Contact: UCD.

November 7-9—**Geriatrics Update: 1994.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Mon-Wed. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INFECTIOUS DISEASE

November 4-5—**Kuzell Institute Symposia for Rheumatology and Infectious Diseases.** California Pacific Medical Center at Ana Hotel, San Francisco. Fri-Sat. 12 hrs. $60. Contact: Kaura Johnson, CPMC, 2485 Clay St, San Francisco. (415) 923-3242.

November 4-6—**Advances in Infectious Disease.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

October 22—**Diabetes.** Sutter Community Hospitals at Sacramento. Sat. Contact: Peggy Coit, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

OB/GYN

October 1—**Colscopy.** Sutter Community Hospitals at Sacramento. Sat. Contacat: Lynne MacRae, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

October 1-2—**6th Annual Ultrasound Update: 1994.** UCD at Red Lion Inn, Sacramento. Sat-Sun. 10 hrs. $240. Contact: UCD.

October 8—**Women's Health.** Sutter Community Hospitals at Stockton. Sat. Contact: Catherine Davis, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

December 1-3—**Obstetrics and Gynecology Conference.** University of Nebraska Medical Center at Bally's, Las Vegas, Nevada. Thurs-Sat. $275. Contact: UNMC, 600 S 42nd St, Omaha, NE 68198-5651. (800) 642-1095 or (402) 559-4152.

February 9-12—**50th Annual Postgraduate OB/GYN Assembly.** Obstetrical and Gynecological Assembly of Southern California at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OGASC, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

ONCOLOGY

October 6-8—**18th Annual Physicians Cancer Symposium.** Scripps Memorial Hospital at Stevens Cancer Center, San Diego. Thurs-Sat. 16.5 hrs. $390. Contact: Cancer Symposium, 2603 Main St, Ste 690, Irvine 92714. (800) 321-6338.

OPHTHALMOLOGY

December 8-10—**New and Practical Approaches to Glaucoma Management.** UCSF at Ritz-Carlton Hotel and UCSF, San Francisco. Thurs-Sat. 13.5 hrs. $200-$395. Contact: UCSF.

December 9-10—**1st Annual West Coast Cosmetic Eyelid Rejuvenation Symposium.** Medical Education Resources at Beverly Hilton, Beverly Hills. Fri-Sat. 14 hrs. $575. Contact: Angela O'Mara, (714) 760-1522.

January 14—**Primary Care Ophthalmology.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

OTOLARYNGOLOGY

October 9-14–November 13-18—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 53 hrs. $875-$1,100. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

November 3-5—**Otolaryngology Update: 1994.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17 hrs. $425. Contact: UCSF.

PATHOLOGY

November 13-16—**Clinical Microbiology Update.** American Society of Clinical Pathologists at Pan Pacific Hotel, San Diego. Sun-Wed. Contact: ASCP, 2100 W Harrison St, Chicago, Il 60612-3798. (800) 621-4142.

December 5-7—**Soft Tissue Pathology: Conceptual and Practical Approaches to Diagnosis.** American Society of Clinical Pathologists at Surf and Sand Hotel, Laguna Beach. Mon-Wed. Contact: ASCP, 2100 W Harrison St, Chicago, IL 60612. (800) 621-4142.

PEDIATRICS

October 1—**Therapy for Childhood Neuromuscular Diseases.** Children's Hospital and Health Center at Hyatt Regency, San Diego. Sat. 6.5 hrs. $75. Contact: CAM, 3030 Children's Way, San Diego 92123. (619) 576-5819.

October 22—**Pediatrics.** Sutter Community Hospitals at Auburn. Sat. Contact: Lynne MacRae, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

October 29—**Ambulatory Pediatrics.** UCD at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. $95. Contact: UCD.

October 29—**Pediatric Otology Update 1994.** Children's Hospital Oakland. Sat. Contact: Hearing Institute Foundation, 2120 Forest Ave, #2, San Jose 95128. (408) 288-7777.

December 1-4—**Society of ENT Advances in Children.** UCD at Radisson Hotel, Sacramento. Thurs-Sun. 10 hrs. Contact: UCD.

December 3—**13th Annual Binational Pediatric Conference.** Children's Hospital San Diego and American Academy of Pediatrics at Mercy Hospital Educational Center, San Diego. Sat. $45. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

December 3-4—**Stabilization and Management of the Critically Ill Child.** UCSF at Mark Hopkins Hotel, San Francisco. Sat-Sun. 9 hrs. $250. Contact: UCSF.

January 21-28—**Pediatric Emergencies.** UCSD at Kona, Hawaii. 21 hrs. $460. Contact: UCSD.

January 23-27—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital San Diego at Town and Country Hotel, San Diego. Mon-Fri. $395. Contact: Children's Hospital, MC 5016, 3020 Children's Way, San Diego 92123. (619) 495-4940.

February 20-22—**Pediatrics Update 1995.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

PHYSICAL MEDICINE/REHABILITATION

October 8-12—**56th Annual Assembly, American Academy of Physical Medicine and Rehabilitation** at Anaheim Hilton Hotel and Towers and Anaheim Convention Center. Sun-Wed. Contact: AAPMR, 122 S Michigan Ave, Ste 1300, Chicago, IL 60603-6107. (312) 922-9366.

PSYCHIATRY

October 7-11—**The Power of the Art: Introduction to Medical Hypnosis and Other Practical Wisdoms.** UCSD at Colonial Inn, La Jolla. Fri-Tues. 26 hrs. Contact: UCSD.

October 14-15—**Psychopharmacology Clinical Research Update.** UCD at Hilton Hotel, San Francisco. Fri-Sat. 14 hrs. $395. Contact: UCD.

January 22-27—**21st Annual Midwinter Program for Psychiatrists.** UCD at Incline Village, Nevada. Sun-Fri. 25 hrs. Contact: UCD.

(Continued on Page 228)

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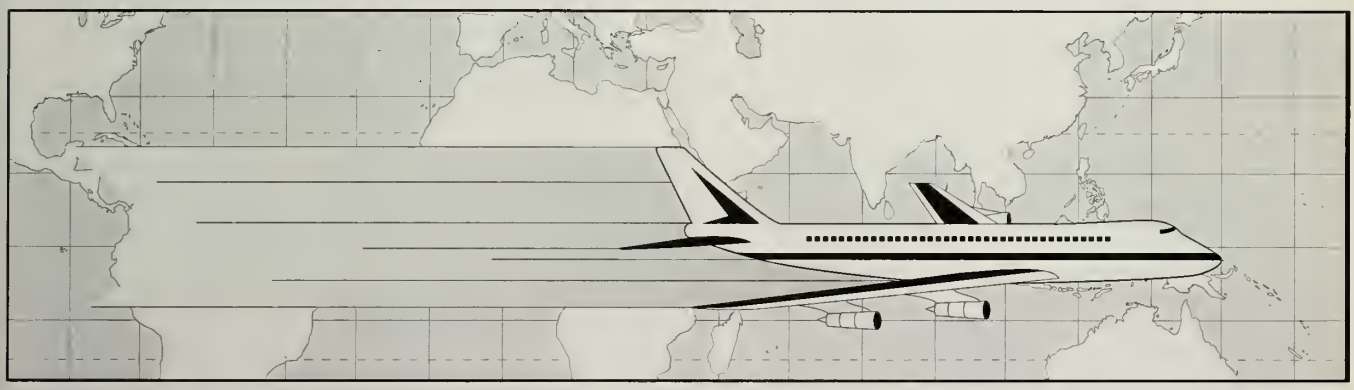

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PULMONARY MEDICINE

October 13-15—**Pulmonary and Critical Care Medicine.** UCSF at Ana Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

February 3-5—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Sheraton Desert Inn, Las Vegas, Nevada. Fri-Sun. 12 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528.

RADIOLOGY

October 2—**Oncologic Imaging Update.** UCSF at Fairmont Hotel, San Francisco. Sun. 6.5 hrs. $150. Contact: UCSF.

October 3-7—**Clinical Magnetic Resonance Imaging.** UCSF at Fairmont Hotel, San Francisco. Mon-Fri. 33 hrs. $595. Contact: UCSF.

October 7-8—**Vascular Ultrasound: State of the Art.** UCSF at Fairmont Hotel, San Francisco. Fri-Sat. 13.5 hrs. $295. Contact: UCSF.

October 10-14—**Neuroimaging Visiting Fellowship Program.** Stanford School of Medicine. Mon-Fri. 40 hrs. Contact: Barbara Platt, (415) 723-4733.

October 15-16—**Neuroradiology Update.** UCSD at Hotel del Coronado. Sat-Sun. Contact: UCSD.

October 17-19—**Radiology for the Non-Radiologist.** UCSD at Hyatt Regency, La Jolla. Mon-Wed. 20 hrs. $450. Contact: UCSD.

October 17-21—**19th Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. Contact: UCSD.

October 21-23—**14th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. Contact: UCSD.

October 31–November 4—**Diagnostic Radiology Seminars.** UCSF at Ritz-Carlton Kapalua, Maui, Hawaii. Mon-Fri. 26 hrs. $595. Contact: UCSF.

November 14-18—**A Practical Approach to Breast Imaging.** UCSF at Ritz-Carlton, Rancho Mirage. Mon-Fri. 20 hrs. $595. Contact: UCSF.

December 8-10—**Magnetic Resonance Angiography in Clinical Practice with CTA Correlation.** UCSF at Ritz-Carlton, Rancho Mirage. Thurs-Sat. 12.5 hrs. $425. Contact: UCSF.

December 11-16—**A Practical Approach to Breast Imaging.** UCSF at Ritz-Carlton Kapalua, Maui, Hawaii. Sun-Fri. 20 hrs. $595. Contact: UCSF.

SLEEP MEDICINE

January 28—**Sleep Medicine: Practices for the 21st Century.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

SURGERY

October 29—**Suture Workshop.** Sutter Community Hospitals at Sacramento. Sat. Contact: Catherine Davis, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

December 8-9—**13th Annual Neurosurgical Nurses' Conference.** UCSF at Hyatt Regency Embarcadero, San Francisco. Thurs-Fri. 13.5 hrs. $325. Contact: UCSF.

January 13-14—**What's New in General Surgery: 17th Annual Postgraduate Course.** UCD at Hyatt Hotel, Sacramento. 15 hrs. Contact: UCD.

GENERAL/MULTIDISCIPLINARY

October 27-30—**1994 CME/Golf Meeting.** Nevada Academy of Family Physicians at Sheraton Desert Inn Hotel & Casino, Las Vegas. Thurs-Sun. 21 hrs. Contact: Barbara Bolling, NAFP, PO Box 27713, Las Vegas, NV 89126-1713. (702) 647-0117.

January 19-22—**Medicine Meets Virtual Reality II: Interactive Technology & Healthcare.** UCSD. Thurs-Sat. Contact: UCSD.

January 31-February 4—**Critical Care by Design.** Society of Critical Care Medicine at Moscone Center, San Francisco. Tues-Sat. 30.5 hrs. $600. Contact: SCCM, 8101 E Kaiser Blvd, Anaheim 92808-2259. (714) 282-6000.

February 13-17—**Physician Heal Thyself.** UCSD at Sheraton Harbor Island, San Diego. Mon-Fri. Contact: UCSD.

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Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

October 24-28—**Prevention in Practice: Workplace Health in the 21st Century.** American College of Occupational and Environmental Medicine at Denver Marriott City Center, Denver. Mon-Fri. Contact: ACOEM, (708) 228-6850.

January 28-February 2—**24th Annual Mid-Winter Conference of Colorado Ophthalmological Society.** Sheraton Steamboat, Steamboat Springs. Sun-Thurs. Contact: David R. Scott, (800) 394-4968.

February 20-24—**19th Midwinter Symposium on Practice Surgical Challenges in Otolaryngology.** University of Illinois College of Medicine at Snowmass. Mon-Fri. Contact: Jane Whitener, (312) 996-5751.

February 26-March 3—**Ninth Annual Cardiology for the Clinician Conference: Practical Guidelines for Merging Advances in Cardiology and Bedside Medicine.** University of Illinois College of Medicine at Snowmass. Mon-Fri. Contact: Sue Talbert, (312) 996-4631.

March 5-10—**15th Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Medical Center, (402) 559-4152 or (800) 642-1095; FAX (402) 559-5915.

July 28-August 1—**80th Annual Summer Conference.** Colorado Ophthalmological Society at Sheraton Steamboat Resort, Steamboat Springs. Fri-Tues. Contact: David R. Scott, (800) 394-4968; FAX (303) 438-9602.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 270-6761.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 5-9—**3rd Annual New Mexico Medical Computer Course.** Holiday Inn Pyramid Hotel, Albuquerque. Contact: Floyd Smith, NMOMA, PO Box 90396, Albuquerque 87199-0396. (505) 828-1905.

October 8-9—**What Is New With the Newborn?** New Mexico Pediatric Society at Snakedance, Taos Ski Valley. Contact: Richard Rolston, MD, (505) 898-7898.

October 28-29—**ECG Interpretation for the Primary Care Physician.** Journal Center, Albuquerque. Fri-Sun. Contact: Tracy L. Green, New Mexico Heart Clinic, (505) 841-1000.

(Continued on Page 230)

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Nov. 94	Orlando, FL	18-20	Anaheim,CA	18-20	St. John, USVI	17-19	Naples, FL	4-6
Dec. 94	Grand Cayman Isl.	1-3	Key West, FL	2-4	Scottsdale, AZ	2-4	Las Vegas, NV	9-11
Feb. 95	Scottsdale, AZ	24-26	Breckenridge, CO	19-21	Las Vegas, NV	3-5	Key West, FL	17-19
Mar. 95	Las Vegas, NV	24-26	Grand Cayman	3/30-4/1	Orlando, FL	3/31-4/2	Squaw Valley, CA	9-11

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(Continued from Page 228)

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

December 2—**AIDS and Related Diseases.** University of Utah School of Medicine. Fri. Contact: UUSM.

December 3-8—**Intensive MR Imaging and Neuroradiology.** University of Utah School of Medicine at the Marriott Hotel, Salt Lake City. Sat-Thurs. 45 hrs; $1,200. Contact: UUSM.

January 17-22—**Advances in Craniofacial/Oculoplastic and Facial Aesthetic Surgery.** University of Utah School of Medicine at the Cliff Lodge at Snowbird. Tues-Sun. 24 hrs; $525. Contact: UUSM.

January 23-27—**Workshops in Advanced MR Imaging, Head and Neck Imaging, and Neuroradiology.** University of Utah School of Medicine. Mon-Fri. Contact: UUSM.

February 6-10—**Surgical Pathology.** University of Utah School of Medicine at the Yarrow Hotel, Park City. Mon-Fri. 20 hrs; $550.Contact: UUSM.

February 20-24—**Workshops in Advanced MR Imaging, Head and Neck Imaging, and Neuroradiology.** University of Utah School of Medicine. Mon-Fri. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS: Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.
UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

October 6—**Sleep Symposium.** Seattle. Thurs. Contact: Providence, (206) 320-2552.

October 12—**Northwest Occupational Health Conference: Competing Influences in Developing Occupational Health Policy.** Bellevue. Wed. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

October 14—**Radiation Oncology Symposium.** Seattle. Fri. Contact: Providence, (206) 320-2552.

October 15—**Arthrocentesis & Injection Techniques.** Seattle. Sat. Contact: U/W.

October 15—**Arthrocentesis & Injection Techniques.** Seattle. Sat. Contact: U/W.

October 15—**Interventional Radiology.** Seattle. Sat. Contact: U/W.

October 20—**Cancer Care Symposium.** Seattle. Thurs. Contact: Providence, (206) 320-2552.

October 21-22—**Transplant Opportunities.** Seattle. Fri-Sat. Contact: Providence, (206) 320-2552.

October 27—**Cancer Care Symposium.** Seattle. Thurs. Contact: Providence, (206) 320-2552.

October 27-30—**7th Annual Pediatric Critical Care Colloquium.** Seattle. Thurs-Sun. Contact: Children's, (206) 526-2501.

October 28-29—**Mental Health Update.** Seattle. Fri-Sat. Contact: U/W.

November 3-4—**Current Concepts in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 4—**Muscular Dystrophy and Related Disorders.** Seattle. Fri. Contact: Children's, (206) 526-2501.

November 10—**Family Practice Symposium.** Seattle. Thurs. Contact: Providence, (206) 320-2552.

November 11-12—**Pediatric Advanced Life Support.** Seattle. Fri-Sat. Contact: Children's, (206) 368-4802.

December 2—**Pediatric Update.** Seattle. Fri. Contact: Children's, (206) 526-2501.

December 7-10—**American College of Physicians.** Seattle. Wed-Sat. Contact: U/W.

December 8-10—**10th Annual Infectious Disease Conference.** Seattle. Thurs-Sat. Contact: Pacific Northwest Medical Education Institute, (206) 261-2160.

March 2—**Emergency Response in the Workplace: An Occupational Health Nursing Update.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

April 13—**Advances in Occupational and Environmental Medicine.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.
PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.
U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.
VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.
WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762. ◆

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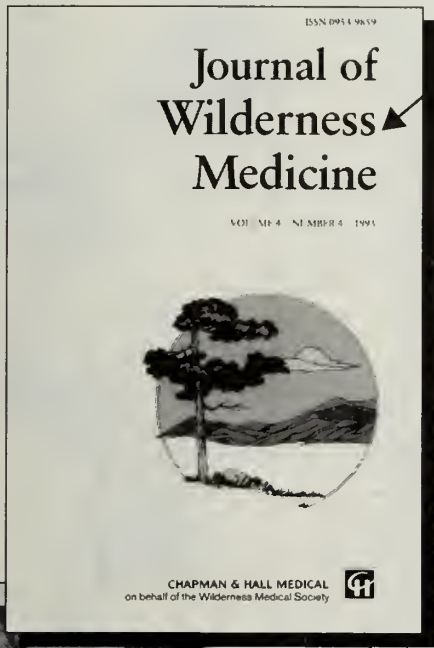
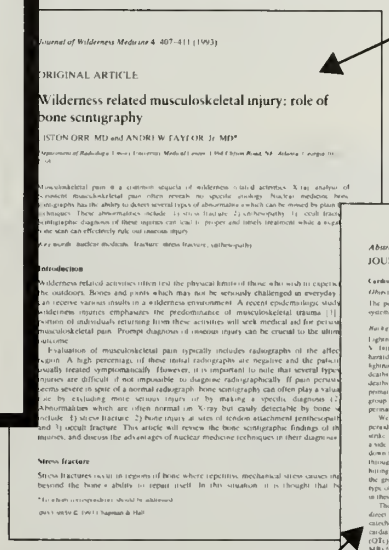


Edited by
Paul S. Auerbach, MD,
Stanford University Hospital,
Stanford, CA; and
Oswald Oelz, MD,
Stadtspital Triemli, Zurich, Switzerland



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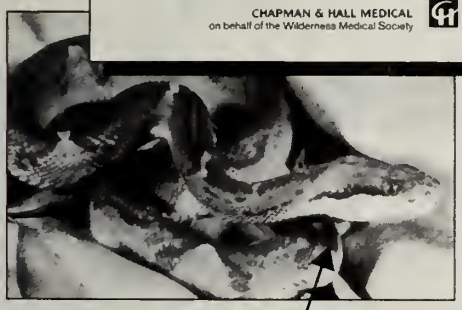
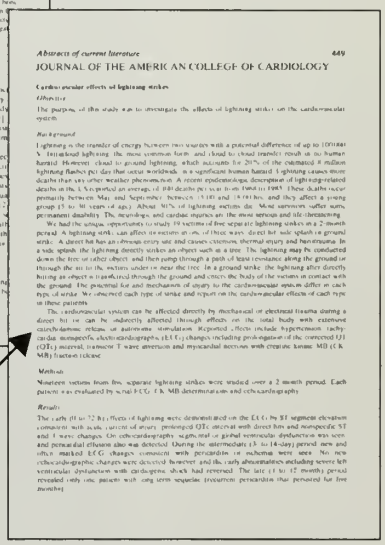


Lachesis muta–the bushmaster.
Review: Central and South American pit vipers.
Davidson et al. JWM Vol. 4, Issue 4, 1993.



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In Memoriam

California Medical Association

BREEDEN, ROBERT R., Weaverville. Died Jul 30, 1994, aged 68. Graduate of Northwestern University Medical School, Chicago, 1949. Licensed in California in 1952. Dr Breeden was a member of the Shasta-Trinity County Medical Society.

❧

CAMPISI, DOMINIC A., San Jose. Died Aug 5, 1994, aged 82. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1937. Licensed in California in 1937. Dr Campisi was a member of the Santa Clara County Medical Association.

❧

GOLDTHWAITE, DANA D., Livermore. Died Jul 1994, aged 79. Graduate of McGill University Faculty of Medicine, Montreal, 1940. Licensed in California in 1966. Dr Goldthwaite was a member of the Alameda-Contra Costa Medical Association.

❧

HINMAN, ALLEN T., San Francisco. Died Jul 9, 1994, aged 85. Graduate of University of California, San Francisco, 1935. Licensed in California in 1935. Dr Hinman was a member of the San Francisco Medical Society.

❧

MCPHERSON, MAHLON D., Santa Cruz. Died Jul 11, 1994, aged 91. Graduate of University of Illinois College of Medicine, Chicago, 1929. Licensed in California in 1930. Dr McPherson was a member of the Santa Cruz County Medical Society.

❧

MOORE, HERBERT L., Arcata. Died Jul 6, 1994, aged 80. Graduate of University of California, San Francisco, School of Medicine, 1940. Licensed in California in 1946. Dr Moore was a member of the Humboldt-Del Norte Medical Society.

❧

PERKINS, CHARLES B., Napa. Died Jul 3, 1994, aged 86. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1933. Licensed in California in 1959. Dr Perkins was a member of the Napa County Medical Society.

❧

ROBINSON, JULIUS C., Richmond. Died Jun 25, 1994, aged 67. Graduate of Meharry College of Medicine, Nashville, Tennessee, 1952. Licensed in California in 1954. Dr Robinson was a member of the Alameda-Contra Costa Medical Association.

SHEEHY, WILLIAM R., Berkeley. Died Jul 9, 1994, aged 75. Graduate of University of Michigan Medical School, Ann Arbor, 1943. Licensed in California in 1944. Dr Sheehy was a member of the Alameda-Contra Costa Medical Association.

❧

WELKE, ELTON G., San Francisco. Died Jul 25, 1994, aged 80. Graduate of University of California, San Francisco, School of Medicine, 1945. Licensed in California in 1945. Dr Welke was a member of the San Francisco Medical Society.

❧

WOODWARD, SHELDON C., Menlo Park. Died Apr 9, 1994, aged 73. Graduate of University of Michigan Medical School, Ann Arbor, 1945. Licensed in California in 1951. Dr Woodward was a member of the San Mateo County Medical Society.

❧

New Mexico Medical Society

HOGSETT, GLADE C., Carlsbad. Died Mar 26, 1994, aged 79. Graduate of University of Colorado School of Medicine, Denver, 1942. Licensed in New Mexico in 1946. Dr Hogsett was a member of the Eddy County Medical Society.

❧

MINEAR, WILLIAM L., Albuquerque. Died May 7, 1994, aged 84. Graduate of Northwestern University School of Medicine, Chicago, Illinois, 1937. Licensed in New Mexico in 1948. Dr Minear was a member of the Greater Albuquerque Medical Association.

❧

SALA, JOSE M., Albuquerque. Died Feb 9, 1994, aged 76. Graduate of Universidad Nacional de Rosario, Argentina, 1944. Licensed in New Mexico in 1975. Dr Sala was a member of the Greater Albuquerque Medical Association.

❧

SAUL, ROBERT J., Mountainair. Died Feb 15, 1994, aged 77. Graduate of Jefferson Medical College, Philadelphia, Pennsylvania, 1943. Licensed in New Mexico in 1949. Dr Saul was a member of the New Mexico Medical Society.

❧

SHARPE, JAMES J., Albuquerque. Died Aug 7, 1994, aged 72. Graduate of Loyola University, Maywood, Illinois, 1950. Licensed in New Mexico in 1953. Dr Sharpe was a member of the Greater Albuquerque Medical Association.

❧

WALTNER, JAMES D., Santa Fe. Died May 31, 1994, aged 47. Graduate of University of Texas Southwestern Medical School, Dallas, 1972. Licensed in New Mexico in 1975. Dr Waltner was a member of the Santa Fe Medical Society.

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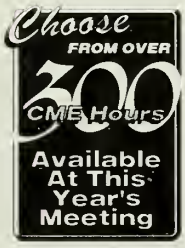

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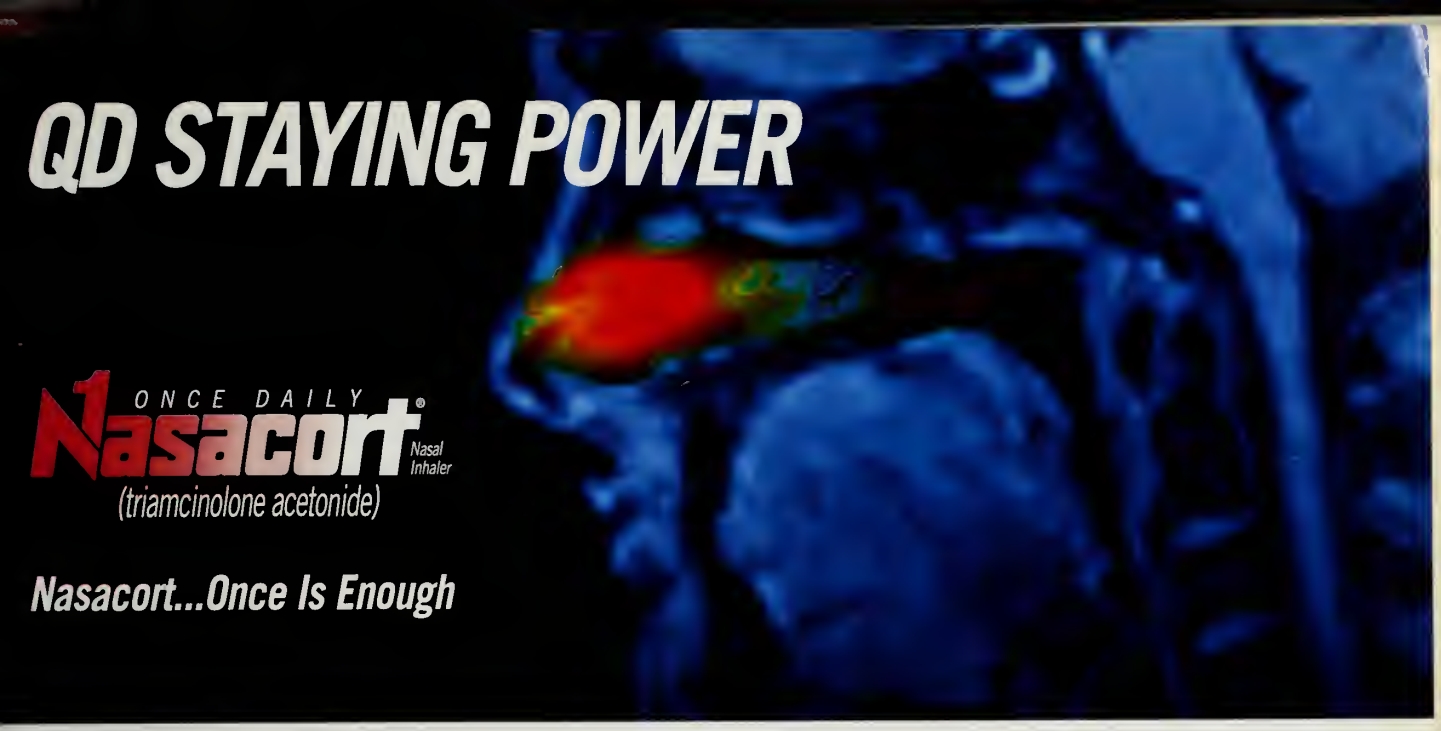

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BRIEF SUMMARY

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, *e.g.*, joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with vancella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

The use of Nasacort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Nasacort Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

PRECAUTIONS

General: In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local therapy and discontinuance of treatment with Nasacort Nasal Inhaler.

Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. Nasacort at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see CLINICAL TRIALS section).

Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances.

When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasacort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients being treated with Nasacort Nasal Inhaler should receive the following information and instructions.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Patients should use Nasacort Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations.

Carcinogenesis, Mutagenesis: Animal studies of triamcinolone acetonide to test its carcinogenic potential are underway.

Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m^2/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m^2/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m^2/day or 110 mcg/m^2/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery. Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5 - 15.0 mcg/kg/day or 20 - 110 mcg/m^2/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m^2/day and 7.0 mcg/m^2/day).

Pregnancy: Pregnancy Category C. Like other corticoids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m^2/day in the rat and 320, 640 and 1280 mcg/m^2/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m^2/day). The doses of 0.02, 0.04, 0.08, and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51, and 318.7 times the minimum recommended dose of 110 mcg of Nasacort per day and 3.2, 6.4, 12.7, and 80 times the maximum recommended dose of 440 mcg of Nasacort per day based on a patient body weight of 70 kg. Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Nasacort Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in children below the age of 12. Oral corticoids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS: In controlled and uncontrolled studies, 1257 patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed Nasacort canister. These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days).

The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received Nasacort. Nasal irritation was reported by 2.8% of the patients receiving Nasacort. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received Nasacort and included: dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects.

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).

OVERDOSAGE: Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects if the nasal application of the 15 mg of triamcinolone acetonide was administered all at once.

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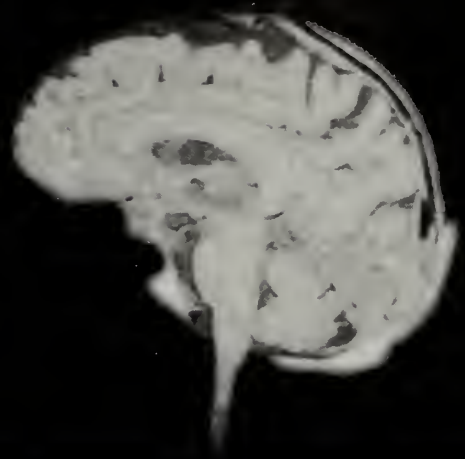

Neurology

THIS SPECIAL ISSUE of THE WESTERN JOURNAL OF MEDICINE takes us from bench to bedside, from cradle (and before) to grave, from diagnosis to treatment, from training to practice. We are taken from the common to the unimaginable, from the past to the future, from theoretical and practical to ethics and policy. Conditions may be acute or chronic and may require intensive care or rehabilitation.

Stephen Hauser, MD, Chair of the Department of Neurology at the University of California, San Francisco, School of Medicine, has been the inspired and inspiring special editor, a visionary leader, and persuader of his distinguished authors. We readers, patients, families, policy makers, and the public are grateful.

LINDA HAWES CLEVER, MD

Introduction

NEUROLOGY HAS ENTERED a new era. Long considered an intellectually rich but therapeutically impoverished discipline, neurologists have traditionally functioned as prestidigitators in the spectacle of medicine, capable of astonishing displays of anatomic localization, pathologic inference and diagnosis, but with services that are ultimately limited to the education of patients or referring physicians. Medical students frequently have been heard to comment that neurology is an interesting but depressing specialty.

In the mass media or in literature, also, we neurologists tend to be treated unkindly. The most frequent image is that of the mad scientist, brilliant but deranged, the villain who exploits neuroscience for evil or twisted purposes: Dr Frankenstein; or Frank MacLeary, cadaveric organ dealer in Robin Cook's *Coma*. On occasion, a more sympathetic image presents neurologists as lovable but disheveled nerds, socially infantile, well-meaning, but ultimately ineffective. We suspect that orthopedists would not have tolerated the public image that neurologists have endured in silence for so long.

I hope that this issue of THE WESTERN JOURNAL OF MEDICINE will contribute in a small way to a changing perception of neurology. Each of three sections will focus on a different aspect of progress and change in the field. A remarkable and distinguished group of contributors will guide readers through this rapidly changing terrain.

Within the past decade, molecular biology has transformed neurology more dramatically and more rapidly than even its most visionary proponents would have dared to predict. Genetic linkage approaches have resulted, as of this writing, in the identification of more than 50 neurologic disease genes and in the chromosomal localization of several hundred more. The genes responsible for some of the most common and mysterious nervous system diseases, including Duchenne-type muscular dystrophy (dystrophin), myotonic dystrophy (CTG repeat 3′ of myotonin), Huntington's disease (huntingtin), Charcot-Marie-

Tooth disease type 1A (PMP-22), and neurofibromatosis type 1 (neurofibromin) have been identified.

Equally exciting is the potential to apply linkage strategies to genetically complex neurologic disorders. In contrast to the single gene disorders discussed here, genetically complex diseases may be polygenic in origin, such as those due to the effects of multiple unlinked genes, or have both a genetic and an environmental component to their pathogenesis. The most spectacular recent discovery in this area has been the demonstration of the apolipoprotein E (apo E) gene effect on Alzheimer's disease. The human apo E gene and protein has four major alleles or forms. The presence of the E-4 allele that occurs normally on approximately 15% of chromosomes is a clear risk factor for sporadic—and some late-onset familial—forms of Alzheimer's disease. How the E-4 allele influences the appearance of Alzheimer's disease is not entirely clear, but it may injure neurons by interacting with the β-amyloid peptide, resulting in neuritic plaque formation, or by destabilyzing the cytoskeletal τ protein and facilitating the development of neurofibrillary tangles.

In the first section of this special issue, entitled "Discovery," several areas of important breakthroughs in the understanding of neurologic diseases are highlighted. The 1990s have been designated by Congress as "The Decade of the Brain." We thus begin with a discussion of the goals of the "Decade of the Brain" project, achievements to date, and prospects for the future. We follow with a summary of advances and challenges facing neurogenetics and with discussions of how growth factors work in the nervous system and the prospects for selective immune manipulation and gene therapy. The spectacular story of prions, a novel genetic and infectious cause of disease, is discussed, as is the molecular understanding of the biology of alcohol abuse. The selection includes a glimpse into developing neuroimaging techniques that permit the study of human brain function in vivo.

The second section, "Therapy," deals with practical aspects of therapy for neurologic diseases. Here we have focused on five categories of nervous system disorders—stroke, multiple sclerosis, headache, Parkinson's disease, and epilepsy—commonly encountered in medicine. For each, important therapeutic developments have raised or are in the process of raising the standard of care that is possible.

The third section, "The New Era," is intended to challenge readers in different ways. Some areas that are explored do not permit complete objectivity, and we apologize in advance for any unintended offense that readers with a different perspective may find on reading this section. The authors explore the place of neurology in the medical world and by extrapolation the ideal number of practitioners that are needed in this specialty. Contributions on neuroimaging, education, neurorehabilitation, and biotechnology are offered. The final chapter attempts to summarize the future clinical role of neurologists in an integrated health care delivery system.

Concern with the size of our specialty is not unique to neurology. It is common to most medical enterprises that are attempting to fit into an evolving health care system. The physicist Freeman Dyson,* writing about the importance of size in nature, observed the following:

> To survive, an animal has not only to be of the right size for the functioning of its internal anatomy. It has also to be of the right size to form a stable community with the bigger and smaller creatures on which it is dependent. In the natural ecology of living creatures, the overwhelming majority of successful animals are small, but the few large animals tend to dominate the landscape. The large animals have an ecological importance that is out of proportion to their numbers. And so it is also in science. The vast majority of successful scientific enterprises are small, but the big enterprises also have an essential role to play. And the big enterprises tend to dominate the political and educational milieu within which the small enterprises must learn to survive. Out of this dominance of the big enterprises arise the central questions of scientific ecology. How should the balance between big and small be maintained? How big is too big and how small is too small? How can we launch large projects without creating political pressures that endanger the integrity of science? . . . We cannot calculate from general principles the optimal size of a scientific project, any more than we can calculate from general principles the optimal size of an elephant or a whale. Every scientific project is unique, just as every species of animal is unique. The purpose of the science of ecology is not to calculate the sizes of elephants and whales but to understand the conditions under which elephants and whales can flourish.

As in science, so it is for medicine. For neurology to flourish, it must do so by creating a proper fit for itself in the modern health care system, in the increasingly competitive world of basic neuroscience research, and in a society whose resources are strained. Neurology must demonstrate the value of its clinical services to patients with neurologic disease, define its role in the education of generalists, and justify its continuing leadership in disease discovery. The authors and I hope that in this special issue, we have conveyed to readers a sense of the excitement, ferment, and promise of the field.

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**On Being the Right Size: Reflections on the Ecology of Scientific Projects,* 1988. Reprinted in *From Eros to Gaia,* Pantheon Books, New York, NY, 1992.

Decade of the Brain
An Agenda for the Nineties

MURRAY GOLDSTEIN, DO, MPH, *Washington, DC*

On July 25, 1989, President George Bush, in response to reports written by the National Advisory Councils of the National Institute of Neurological Disorders and Stroke and the National Institute of Mental Health and at the urging of Congress, signed a presidential declaration designating the 1990s to be the "Decade of the Brain" and called on the United States to observe the decade with appropriate activities. At mid-decade, scientific accomplishment has been spectacular; however, both public support and increases in research resources have been minimal. It can be anticipated that scientific progress will continue to be impressive for the remainder of the decade, but many research opportunities will either not be addressed or will be postponed. At mid-decade, the time has come to re-evaluate the research agenda and the public strategy for the remainder of the decade.

(Goldstein M: Decade of the brain—An agenda for the nineties, *In* Neurology—From Basics to Bedside [Special Issue]. West J Med 1994; 161:239-241)

In the closing years of the 1980s, a small group of scientists, science administrators, and political observers met to discuss how the remarkable advances and the opportunities for further progress in the basic and clinical neurologic sciences could be brought to the attention of the public and its elected representatives. It was agreed the time was opportune to initiate an identified national research endeavor that would describe attainable neuroscientific objectives pertinent to health issues. The opportunities available for addressing these research objectives would be documented, and the additional resources necessary to meet these goals would be described. The effort needed an identity, a focal point for program implementation, and champions both within and outside of government. Questions addressed were, Should the effort follow the format of an open-ended endeavor such as the War Against Cancer, or a time-limited megaproject such as the Genome Project, or something else? Who could be the champions within government? Should the effort be supported outside of government by a structured coalition of professional, scientific, and lay organizations, or should each organization be urged to mobilize its own forces to support the endeavor?

The result of these discussions gave birth in 1988 to the concept that the 1990s be designated the "Decade of the Brain"—a national research endeavor to better understand how the brain (and nervous system) is organized, how it functions, why it fails to function, and what can be done to prevent and treat dysfunction. The proposal would have measurable objectives, describe the need for additional resources, designate a time frame long enough to permit accomplishment, and use language that was understandable and appealing.

In designating program responsibility, the two organizations that already had major responsibility for brain research were proposed to be the focal points for planning and implementation: the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Mental Health (NIMH). Allies needed to be identified who would champion the program both in the administration (the Office of the President or the Office of the Secretary of the Department of Health and Human Services) and in Congress. These leaders would need the support and assistance of nongovernmental organizations that could collaborate as a national coalition.

The stage was set, the objectives defined, the roles enumerated, and the clock started ticking.

The Next Step

In July 1988, the National Advisory Councils of the

From the United Cerebral Palsy Research & Educational Foundation, Washington, DC.
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ABBREVIATIONS USED IN TEXT

NIH = National Institutes of Health
NIMH = National Institute of Mental Health
NINDS = National Institute of Neurological Disorders and Stroke

NINDS and the NIMH organized working groups of scientists to specify research targets, research opportunities, and the resources required to meet these targets in their respective areas of research responsibility. Several attempts to have a joint NINDS-NIMH effort and a single national plan failed. The reasons for failure are complex and disappointing; however, the leadership of both institutes agreed that their organizations would develop plans and would share information on a continuing basis. Both groups developed and published their plans.[1,2]

A champion in the administration to spearhead these initiatives was never recruited. Health and science leaders in the administration were cautious because of the increasing fiscal deficit and the desire to maintain an adequate across-the-board research endeavor at the National Institutes of Health (NIH). They feared that in a period of a level budget for the NIH, specified increases in one area would be at the cost of other health research areas, as was already being threatened by grassroots activism for additional research funds for the acquired immunodeficiency syndrome and Alzheimer's disease. Thus, administration executives did not say no to a Decade of the Brain; they remained silent.

The Republican leader on the House Appropriations Subcommittee responsible for the NIH budget, Representative Silvio Conte (Republican, Massachusetts), took the initiative to be the congressional champion for the Decade of the Brain. In a "Dear Colleague" letter, he asked that the House of Representatives join him in requesting that the 1990s be designated by the President as the Decade of the Brain; Senator Donald W. Riegle (Democrat, Michigan) did the same in the Senate. Because of their efforts and the resulting House Joint Resolution 174, on July 25, 1989, President Bush signed a presidential declaration calling on the United States to observe the Decade of the Brain with appropriate activities.

Professional, scientific, and lay organization leaders hailed this presidential declaration and urged their constituencies to write their representatives in Congress for the additional resources necessary to implement the program. Despite the declaration, the President's budget for the next fiscal year (1990) did not propose increased funding to implement an accelerated research program. At the congressional level, a modest increase was provided for both the NINDS and NIMH. The Decade of the Brain was born—but with a whimper rather than a lusty cry.

Another Step

On the advice of friends in high places, the NINDS Advisory Council decided that a definitive action plan was needed to meet more specific research targets. With the help of the scientific community and following public hearings on needs and priorities, a follow-up report was developed and published.[3] The NINDS Implementation Plan was arranged in sections addressing research opportunities for advances in critical neurologic health areas: the developing brain (developmental disorders); the injured brain (head and spinal cord trauma); the failing brain (multiple sclerosis); and the feeling brain (pain). A special section on training was also included. The plan was distributed to the Executive Office and Congress in June 1990 as final discussions were being held for the 1991 budget. It was also made available to nongovernmental organizations and widely distributed by them to their constituencies. There were discussions among scientific and health organization leaders about a coordinated national grassroots effort to influence Congress, but it did not materialize; instead, a handful of letters in support of a substantial increase in funds for neuroscientific research was sent to Congress by the leadership of several professional and public organizations.

The NINDS Implementation Plan was accepted by the Bush Administration and congressional leaders and was praised as a "blueprint" and as a planning "model." The appropriation in the 1991 budget for both the NINDS and NIMH again provided only a modest increase in support of the second year of the decade, however. The Decade of the Brain moved forward, but as part of the normal order of things rather than with gusto. The following reasons were given: fiscal constraint (was this a reason or an excuse?), insufficient scientific community support (was this a problem of mixed loyalties and divided support?), lack of grassroots community activism (or was this a concern with individual diseases and preoccupation with health care services?), and poor leadership (or were there too many leaders?).

The Issues

Meanwhile, despite financial limitations, research did progress. Cell and molecular biology were now the everyday language of neurologic research. The identification of the genetic loci for neurologic function and neurologic dysfunction was ahead of other areas of genetic research. Morphologic and dynamic brain imaging was providing technologies that made the in vivo study of the human brain a reality. The methods of controlled clinical trials were being used to re-evaluate the efficacy of established clinical therapies and to test the applicability of new clinical interventions.

Midpoint

At its midpoint, the Decade of the Brain is an overwhelming scientific success. Basic and clinical neurologic science is identified as an important component of the national research agenda. In government, about $1.5 billion is dedicated to research on the nervous system, principally through the programs of the NIH. A modest growth in neuroscientific support continues, but with increasing competition for available resources. Neuroscience continues to be an exploration, providing better insight into the what and the how of the nervous system

in order to address the future; unlike a war, it is not offering quick fixes to problems of the present. The intellectual and the clinical results have already had a profound effect on the promotion of health and the treatment of disease.

Neurologic research is a scientific success story. Four decades of generous support and encouragement have resulted in accomplishments that could hardly be imagined. Then why are we neuroscientists so gloomy? Our problem is that we are frustrated. We recognize that with a meaningful increase in resources, the opportunity for accelerated achievement is possible. This is true in both the basic and the clinical neurologic sciences. As a public force, the neuroscientific community has not been able to share this recognition of opportunity with the President or Congress. This is the frustration—a failure not in scientific accomplishment, but rather in influencing the public and its leaders. The opportunities for important research continue to increase, the training pipeline is providing additional highly skilled basic and clinical scientists, and funding levels are stable. The result is that competition for research funding will become even more intense.

What Next?

How do we approach the second half of the Decade of the Brain? There are three options for the neuroscientific community to consider:

- Remobilize and attempt to obtain support for the additional resources necessary to accelerate a broad-based research program;
- Work to maintain the resources now available so that other research areas targeted to emotional issues do not grow at the expense of neuroscience research; and
- Document the imperative of addressing research on specific neurologic diseases with earmarked additional resources.

The first option is the ideal, but it requires grassroots support or faces the danger of receiving yawning attention. The second option would maintain the status quo and has a reasonable probability of success because of continuing achievements. The third may be successful but only if grassroots support is aggressive; however, it means an increase in targeted, directed research—perhaps at the cost of investigator-initiated research.

An additional issue is organizational. Could more be done by using available resources more effectively? Does the current administrative structure of the NIH provide the best base for implementing a neuroscience research agenda, two major neuroscientific institutions, and three to five others? Are the collaboration and cooperation of the various agencies of the federal government effective, and are they taking advantage collectively of neuroscience research opportunities? Has the time come to reconsider the present loose administrative structure for the support of neuroscientific research and centralize responsibility as is done in the cancer and heart research areas?

How do we maintain the present successful scientific effort and also take advantage of exciting new opportunities? How do we use available resources wisely? How do we get the vigorous support of the public and its representatives? These were the questions asked in the late 1980s when the Decade of the Brain was conceived as a national research initiative. They need to be asked and answered again at the midpoint of the decade.

We have not hit all the bull's-eyes. But a sage has shared this wisdom with me—if you hit all the bull's-eyes, the target was too close.

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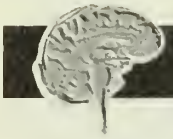

Neurogenetics
Triumphs and Challenges

PENNY GREENSTEIN, MB BCh, *and* THOMAS D. BIRD, MD, *Seattle, Washington*

During this century our understanding of some of the most important and mysterious genetic diseases of the nervous system has blossomed. The advances began slowly by the meticulous collection and detailed description of families with mendelian-inheritance syndromes and those that did not clearly fit any known inheritance pattern. Once the phenotypes of these disorders had been characterized, the enormous task still remained to correlate phenotype with genotype and to uncover the pathophysiologic mechanisms underlying these fascinating diseases.

In this review we briefly describe some of the major advances in the molecular genetics of neurologic disorders. The approach we have taken is genetic rather than anatomic. We have classified neurogenetic disorders into broad categories of gene function (Table 1). This classification is by no means complete because we do not understand how all these genes function (for example, those entitled "trinucleotide repeats"). Furthermore, only genes that were most recently discovered by recombinant DNA technology have been listed. This classification would have been impossible to do less than a decade ago and is testimony to the progress of the past few years.

A major influence on the discovery of these disease genes was the strategy of "reverse genetics," now known as positional cloning. Genetic diseases were first assigned to specific chromosomal regions using normally occurring but variable DNA polymorphisms—restriction fragment-length polymorphism and microsatellite CA repeats—and genetic linkage analysis.[1-3] Sophisticated and continually developing genetic technology has then been able to isolate and identify specific genes and the proteins for which they code.

As a first example, there has been great interest in the genetic basis of Alzheimer's disease. It is now clear that this disease has multiple causes and that familial Alzheimer's displays nonallelic heterogeneity of at least four types. One rare form that occurs early is linked to chromosome 21q with mutations in the amyloid precursor protein gene.[4-6] A second locus at chromosome 14q24.3, with an as-yet-unidentified gene, accounts for more than 70% of families with early-onset familial Alzheimer's disease.[7] A third locus for late-onset Alzheimer's has been identified on chromosome 19q.[8] This has evoked considerable interest because this region contains the gene for apolipoprotein E, which is involved in cholesterol transport to the brain.[9] Furthermore, investigators have found evidence for a genetic association between the $\epsilon 4$ allele and late-onset Alzheimer's disease.[9] There are two possible interpretations of this genetic evidence. The first is that the $\epsilon 4$ isoform of the apo E protein is the chromosome 19 gene that increases the risk of Alzheimer's disease. The second interpretation is that a gene or DNA segment in close proximity and in linkage disequilibrium with the apo E gene is the true risk factor. It remains unknown how apo E relates to the pathogenesis of Alzheimer's disease. Finally, a fourth locus for the disease among families of Volga-German descent resides on a chromosome other than 14, 19, or 21.[10] The identification of these three genes will shed new light on the formation of neuritic plaques and neurofibrillary tangles in cerebral cortex and the causes of this most common form of severe dementia.

Amyotrophic lateral sclerosis (ALS) is an inexorably progressive and ultimately fatal degeneration of motor neurons in cortex, brain stem, and spinal cord that occurs in adults. About 5% to 10% of all cases are familial and often inherited in an autosomal dominant manner. Investigators have shown convincingly that one form of familial ALS is caused by mutations in the superoxide dismutase 1 *(SOD1)* gene, which encodes the cytosolic superoxide dismutase.[11] This enzyme catalyzes the conversion of superoxide into hydrogen peroxide and therefore functions as a "free-radical scavenger." Emerging insights into mechanisms of neuronal injury related to excitotoxicity point to ways in which free radicals may contribute to the gradual death of motor neurons in this disease. Possible treatment strategies can now be proposed, such as blocking of the kainate or α-amino-3-hydroxy-5-methyl-4-isoxasolepropionate receptors, a more effective buffering of calcium entry into the cell, or enhancing the repertoire of free-radical scavengers.

(Greenstein P, Bird TD: Neurogenetics—Triumphs and challenges, *In* Neurology—From Basics to Bedside [Special Issue]. West J Med 1994; 161:242-245)

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TABLE 1.—*Newly Discovered Neurologic Disease Genes*

Gene Class	*Disease*	*Protein*	*Chromosome*
Structural genes	Duchenne's muscular dystrophy	Dystrophin	Xp21.2
	Becker's muscular dystrophy	Dystrophin	Xp21.2
	Paramyotonia congenita	Sodium channel	17q23.1-q25.3
	Hyperkalemic periodic paralysis	Sodium channel	17q23.1-q25.3
	Myotonia congenita	Chloride channel	7q35
	Charcot-Marie-Tooth disease type 1A	PMP-22	17p11.2
	Hereditary neuropathy with liability to pressure palsies	PMP-22	17p11.2
	Charcot-Marie-Tooth disease type 1B	P_0 Myelin	1q21.2-q23
	X-linked Charcot-Marie-Tooth disease	Connexin	Xq13
	Alzheimer's disease	Amyloid precursor	21q21.3-q22.05
	Retinitis pigmentosa	Rhodopsin	3q
	Startle disease (hyperreflexia)	Glycine receptor	5q
Tumor suppressor genes	Neurofibromatosis type 2	Merlin	22q11.21-q13.1
	Neurofibromatosis type 1	Neurofibromin	17q11.2
	Retinoblastoma*	Rb	13q14.1-q14.2
	Von Hippel-Lindau disease (retinocerebral angiomatosis)*	Unknown	3p25
	Tuberous sclerosis	Tuberin	16p13.3
Transport protein genes	X-linked adrenoleukodystrophy	ALDP	Xq28
	Menkes's syndrome (kinky-hair syndrome)	Copper transport protein	Xq13.3
	Wilson's disease (hepatolenticular degeneration)	Copper transport protein	13q14.3
Trinucleotide expansion genes	Fragile X mental retardation	FMR1	Xq27.3
	Huntington's disease (hereditary chorea)	Huntingtin	4p16.3
	Myotonic dystrophy	Myosin kinase	19q13.3
	Spinocerebellar atrophy type 1	Ataxin 1	6p23-24
	Kennedy's spinal bulbar muscular atrophy	Androgen receptor	Xq21.3-q22
	Dentato-rubral-pallido-luysian atrophy	Unknown	12
Cell protection genes	Familial amyotrophic lateral sclerosis	Superoxide dismutase (SOD1)	21q22.1-q22.2
Signaling molecules	Charcot-Marie-Tooth disease type 1B	P_0 Myelin	1q21.2-q23
	Miller-Dieker syndrome	G proteins	17p13.3
	Retinitis pigmentosa	Rhodopsin	3q
Mitochondrial genes	Leigh's disease (subacute necrotizing encephalomyelopathy)	Oxidative phosphorylation pathway	
	Myoclonic epilepsy with ragged red fibers	Oxidative phosphorylation pathway	
	Mitochondrial encephalopathy with lactic acidosis and stroke-like syndrome	Oxidative phosphorylation pathway	
	Leber's optic atrophy	Oxidative phosphorylation pathway	
	Kern Sayer's disease	Oxidative phosphorylation pathway	
Prion proteins	Creutzfeldt-Jakob disease	Prion	20pter-p12
	Gerstmann-Straussler-Sheinker syndrome	Prion	20pter-p12
	Familial fatal insomnia	Prion	20pter-p12

*These can also be classified as cell cycle genes.

Neurofibromatosis is one of the most common inherited disorders of the nervous system, affecting 2 to 3 million people worldwide. In 1987 linkage analysis mapped the *NF1* gene to chromosome 17, and the defective gene was discovered in 1990.[12] It acts as a "recessive tumor suppressor" whose loss of function appears to be associated not only with typical *NF1* tumors, but also with a variety of seemingly unrelated sporadic cancers in the general population, including sporadic astrocytomas (unrelated to *NF1*), neuroblastoma, malignant melanoma,[13] colon carcinoma, and the myelodysplastic syndrome. Neurofibromin, the *NF1* protein, appears to act within the cell by inhibiting $p21^{RAS}$ activity, an important mediator of signal transduction in the mitogenic signaling pathway. It also appears to act as a downstream effector of $p21^{RAS}$ activity in the differentiation pathway.[14] Furthermore, neurofibromin may have various cellular functions, independent of its $p21^{RAS}$ guanosine triphosphatase-activating-protein-like activity. Its role as a tumor suppressor is a complex biologic problem beyond the scope of this article, but the data suggest that mechanisms through which mutations in the *NF1* gene may contribute to tumorigenesis are similar to the retinoblastoma model in which both copies of the tumor suppressor locus have to be deleted or otherwise "inactivated" to lead to tumor formation (the "two-hit" model suggested by Knudson).[14,15] The challenge for the future will be to delineate the role of *NF1* in tumorigenesis and as an important regulator of growth and differentiation both within and beyond the nervous system.

X-linked adrenoleukodystrophy is the most common inherited peroxisomal disorder. Recently it has received public attention regarding "Lorenzo's oil" as a possible therapeutic agent for this devastating childhood demyelinating disease.[16] It is characterized by the accumulation of very-long-chain fatty acids because of impaired β-oxida-

tion in peroxisomes. Recent cloning of the gene mutated in some adrenoleukodystrophic families has found that it encodes a protein with homology to a 70K peroxisomal membrane protein.[17] Both this previously known protein and the newly discovered adrenoleukodystrophy protein belong to the adenosine triphosphate-binding cassette transporter protein superfamily involved in the transport of a wide variety of ligands into the peroxisome. Thus, the hypothesis that the adrenoleukodystrophy protein is a peroxisomal transport protein directly involved in the import of very-long-chain fatty acid-coenzyme A synthetase into the peroxisome is novel and appealing and may in the future offer different targeted strategies for treatment.

In a similar vein, the genes that are mutated in Menkes's[18,19] and Wilson's diseases[20] have also been shown to encode proteins with specific copper-binding motifs involved in the transport of copper into and out of cells, respectively.

In addition to the nuclear genome, there exists a much smaller genome in mitochondria. The sequencing of this genome and the identification of mutations within it have clarified several complex multisystem neurologic disorders.[21] Mitochondrial DNA encodes 13 of the 67 or so subunits of the respiratory chain and the oxidative phosphorylation system. It differs from nuclear DNA in that it contains very little noncoding sequence, and it shows a different mode of inheritance from one generation to the next. Mitochondrial DNA is entirely maternally inherited, and interestingly, can still be generated in postmitotic cells—neurons and muscle. As a representative example, the mutation found in myoclonic epilepsy with ragged red fibers is an A-G point mutation at the 8344 locus in the mitochondrial genome.[21] In this condition abnormal mitochondria gather in the outer sarcolemmal membrane to generate the histologic features of "ragged red fibers." Affected persons may have seizures, tremor, ataxia, or weakness in any combination and of widely varying severity. It remains a challenge to explain the broad phenotypic heterogeneity, delayed onset, and the varying degrees of severity, now thought to be due, in part, to the proportion of mutant mitochondrial DNA in blood and other tissues.[22] Knowing that these are mitochondrial diseases has also led to new hypotheses for treatment.

Another article elsewhere in this issue discusses the molecular biology of prion-associated diseases.* Suffice to say that the discovery of genetic disorders that can be both inherited as traditional dominant mutations and transmitted by tissue transplant has opened an entirely new chapter in the study of human biology.

Most recently, the discovery of disease genes related to unstable trinucleotide repeat expansions has raised some fundamental questions about the pathogenesis of inherited diseases.[23] To date, six neurologic disorders have been found associated with these expansions (see Table 1). With several of these conditions, including myotonic dystrophy[24,25] and Huntington's disease,[25] successive generations sometimes display a younger age of onset and increased severity. This phenomenon has been called anticipation and generally correlates with an increasing number of trinucleotide repeats in each generation. Unanswered questions include why the repeat expansions are unstable, how they disturb the function of the encoded proteins, and why larger expansions correlate with more severe clinical disease. The ability to detect the presence of an expanded trinucleotide repeat has rapidly led to commercial diagnostic tests for Huntington's, myotonic dystrophy, and fragile X mental retardation. This has raised ethical and social issues that need to be carefully addressed. We now have the ability to diagnose the carrier state of neurogenetic disorders many decades before symptoms occur. The diseases are largely untreatable and, in the case of Huntington's disease, relentlessly progressive and life shortening. Consequences for insurance, employment, self-esteem, peer acceptance, and prenatal and childhood testing are yet to be fully appreciated and clarified.

This brief review of neurogenetic diseases highlights the remarkable advances of the past few years. It is a tribute to the preceding decades of preparation by clinicians and pathologists, now being capitalized on by molecular biologists. Many challenges remain. There are more genes to be found, mechanisms to be elucidated, diagnostic tests to be refined, treatments and preventions to be discovered, and patients to be healed.

*S. B. Prusiner, MD, "Neurodegeneration in Humans Caused by Prions," on pages 264-272.

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NEUROLOGY Discovery

Neurotrophic Factors and Neurologic Disease

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Discovered only 40 years ago, nerve growth factor is the prototypic neurotrophic factor. By binding to specific receptors on certain neurons in the peripheral nervous system and brain, nerve growth factor acts to enhance their survival, differentiation, and maintenance. In recent years, many additional neurotrophic factors have been discovered; some are structurally related to nerve growth factor while others are distinct from it. The robust actions of neurotrophic factors have suggested their use in preventing or lessening the dysfunction and death of neurons in neurologic disorders. We review the progress in defining neurotrophic factors and their receptors and in characterizing their actions. We also discuss some of the uses of neurotrophic factors in animal models of disease. Finally, we discuss how neurotrophic factors could be implicated in the pathogenesis of neurologic disorders.

(Holtzman DM, Mobley WC: Neurotrophic factors and neurologic disease, *In* Neurology—From Basics to Bedside [Special Issue]. West J Med 1994; 161:246-254)

Neurotrophic factors are polypeptides that exert their actions through binding and activating specific cell surface receptors. It is increasingly apparent that neurotrophic factors have an important role in the growth, development, and maintenance of neurons in both the central and peripheral nervous systems. Evidence accumulated over the past few years points to the existence of a number of classes of neurotrophic factors and documents their remarkable potency on responsive neurons (Table 1). These data are enhancing and accelerating efforts to apply neurotrophic factors to the treatment of human neurologic disease. In this article we briefly discuss the neurotrophic factors most likely to be used in clinical studies in the near future. The structure and functions of these molecules and their receptors are reviewed. Thereafter we consider data from three experiments in which neurotrophic factors have been used in animal models of neurologic disease and the mechanisms by which neurotrophic factors may be implicated in neurodegeneration and its treatment.

TABLE 1.—*Neurotrophic Factors—A Partial Listing*

Factor	*Abbreviation*
Neurotrophins	
Nerve growth factor	NGF
Brain-derived neurotrophic factor	BDNF
Neurotrophin 3	NT-3
Neurotrophin 4/5	NT-4/5
Ciliary neurotrophic factor	CNTF
Leukemia inhibitory factor	LIF
Insulin and the insulinlike growth factors	IGF-I IGF-II
Tumor growth factor-β family	TGFβ
Glial cell line-derived neurotrophic factor	GDNF
Fibroblast growth factors	FGF-1 FGF-2 FGF-5
Epidermal growth factor	EGF

Neurotrophic Factors

Nerve Growth Factor and the Neurotrophins

The neurotrophic factors in the neurotrophin gene family consist of nerve growth factor (NGF), the best characterized member, brain-derived neurotrophic factor (BDNF), neurotrophin (NT)-3, and NT-4/5. Nerve growth factor was discovered by Levi-Montalcini and Hamburger in the late 1940s and early 1950s. They were examining the effect a target has on its innervating neural center and discovered that a particular mouse sarcoma evoked dramatic hypertrophy of innervating dorsal root ganglia and sympathetic ganglia. The authors noted substantial deviations from the normal pattern of embryonic development in the extent of ganglion hyperplasia, the involvement of ganglia distant from the site of the sarcoma, and the bizarre, excessive innervation of various viscera.[1] These findings led to the hypothesis that the neoplastic cells released a soluble, diffusible agent that promoted the differentiation and growth of sympathetic and sensory neurons. This idea was supported in experiments in which the mouse sarcoma elicited the same effects when transplanted onto the chorioallantoic membrane of chick em-

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ABBREVIATIONS USED IN TEXT

BDNF = brain-derived neurotrophic factor
cDNA = complementary DNA
CNTF = ciliary neurotrophic factor
GABA = γ-butyric acid
GDNF = glial cell line-derived neurotrophic factor
IGF-I, -II = insulinlike growth factors I, II
IL-6 = interleukin-6
LIF = leukemia inhibitory factor
mRNA = messenger RNA
NGF = nerve growth factor
NT-3, -4/5 = neurotrophins 3, 4/5

bryos, a location that allowed diffusion through the circulation but prevented direct contact between the sarcoma and developing tissue.[2] Levi-Montalcini and Hamburger called the diffusible agent nerve growth factor. They were later able to purify the material to homogeneity and discovered a rich source that permitted many subsequent investigations on its biology and chemistry.[3]

Nerve growth factor is a 118-amino acid polypeptide that acts on neurons in both the peripheral and central nervous systems. Responsive peripheral neurons include cells in the trigeminal sensory ganglion, dorsal root ganglia, and paravertebral sympathetic ganglia. Nerve growth factor also acts on adrenal chromaffin cells. In the central nervous system, two populations respond robustly to NGF. These are the cholinergic neurons of the basal forebrain and those of the caudate putamen.[3] Nerve growth factor activates responsive cells through binding to specific receptors on their surface.[4] One of these receptors is $p75^{NGFR}$. This glycosylated transmembrane protein binds NGF with low affinity. It appears to modulate NGF binding, but it is not yet clear how and to what extent it influences NGF signaling.[3] Another transmembrane glycoprotein, trkA, serves as a receptor for NGF. The intracellular domain of trkA encodes a tyrosine kinase (Figure 1). The binding of NGF to trkA causes it to dimerize; this activates its kinase and leads to autophosphorylation. Activating trkA kinase is necessary for transmitting the NGF signal.[4,5] Signal transduction is mediated through the phosphorylation of specific residues on trkA. These serve to bind and to activate other proteins, including phospholipase C-γ and phosphatidylinositol 3-kinase.[6,7] The signaling cascade produced by NGF is continued by a number of events, including the activation of other kinases and the generation of second messengers. The details of this cascade are only beginning to be discovered.

In both the peripheral and central nervous systems, NGF is produced in the target of innervating neurons.[3] There are clear examples where neurons have access to NGF mainly through contact with their targets. An interesting requirement imposed by this arrangement is the need to convey the NGF signal down the axon to the cell body. How this is achieved is not yet clear.[6] What is clear is that NGF signaling requires binding to trkA. In every case, NGF-responsive cells have been shown to bear trkA receptors. Thus, it appears that NGF produced in the target of developing and mature neurons binds to trkA on the neurites of these cells to initiate or maintain trophic relationships.

Brain-derived neurotrophic factor (BDNF) was discovered in 1982 as the culmination of a painstaking series of studies by Barde and colleagues.[8] It is a neurotrophic factor similar in structure to NGF. Indeed, the discovery of BDNF suggested the existence of a neurotrophin gene family. This neurotrophic factor is a 120-amino acid polypeptide that is 50% identical to NGF at the amino acid level. The sequence homology was used by several groups to isolate a third member of this family, neurotrophin 3 (NT-3),[9-13] and a fourth member, neurotrophin 4/5 (NT-4/5).[14-16] Cells in the peripheral nervous system that are responsive to BDNF include sensory neurons in the nodose ganglion and a subpopulation of dorsal root ganglia neurons. Brain-derived neurotrophic factor also acts on trigeminal mesencephalic neurons. Its targets in the central nervous system include retinal ganglion neurons, hippocampal neurons, basal forebrain cholinergic neurons, basal forebrain γ-aminobutyric acid (GABA)-ergic neurons, and GABAergic neurons of the ventral mesencephalon.[17,18] Recent studies have demonstrated that BDNF also acts on motoneurons.[19-22] This neurotrophic factor is found predominantly in the central nervous system, where it is most abundant in the adult. The highest levels of BDNF messenger RNA (mRNA) were found in the hippocampus, cortex, and cerebellum.[23] In situ hybridization histochemistry has localized BDNF mRNA to neurons in several brain regions. These include pyramidal, hilar, and dentate granule neurons of the hippocampus and neurons in the neocortex.[24] As with NGF, $p75^{NGFR}$

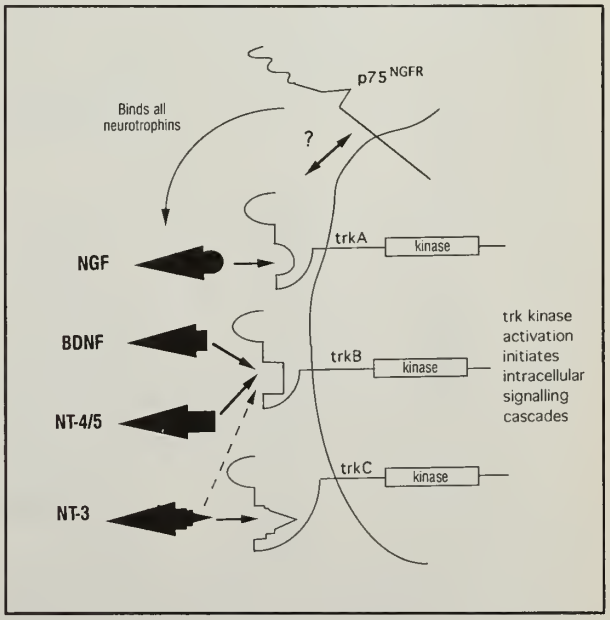

Figure 1.—The diagram illustrates the trk receptors and their specificities for the neurotrophins—nerve growth factor (**NGF**), brain-derived growth factor (**BDNF**), and neurotrophin (**NT**)-3 and NT-4/5. Ligand binding induces dimerization and autophosphorylation that activates signaling. The role of the low-affinity NGF receptor ($p75^{NGFR}$), which binds to all of the neurotrophins, is uncertain.

serves as a receptor for BDNF and binds this neurotrophic factor with low affinity. Another member of the trk gene family, trkB, is the signaling receptor for BDNF (Figure 1). Transcripts of trkB are found in many central nervous system regions, including hippocampus, basal forebrain, neocortex, ventral mesencephalon, and in spinal cord motoneurons.[6,18,24,25] There is an important distinction with respect to trkA and trkB: there are trkB transcripts that encode truncated proteins in which the tyrosine kinase domain is missing.[6] This finding raises the possibility that not all BDNF binding would lead to signaling.

Neurotrophin 3 is the third member of the neurotrophin family. Neurons responsive to NT-3 include cells in both the peripheral and central nervous systems. Among responsive peripheral cells are neurons of the dorsal root ganglia and nodose ganglion and possibly the sympathetic ganglia. In the central nervous system, NT-3-responsive cells include neurons of the trigeminal mesencephalic nucleus, hippocampus, and dopaminergic and GABAergic cells in the ventral mesencephalon.[17,18,26] Motoneurons of the spinal cord also respond.[21] In the peripheral nervous system, NT-3 mRNA is found in muscle. In the central nervous system, high levels of NT-3 mRNA are found in the hippocampus and cerebellum. Neurotrophin 3 mRNA has also been detected in the olfactory bulb, neocortex, diencephalon, midbrain, and spinal cord.[21,24] By in situ hybridization, NT-3 mRNA has been localized to neurons,[24] including embryonic motoneurons.[21,27] Like other neurotrophins, NT-3 binds to $p75^{NGFR}$. Interestingly, it acts by binding to yet another member of the trk family, trkC (Figure 1). Gene expression for trkC is widespread in the central nervous system, with high levels of trkC mRNA in the hippocampus, neocortex, and cerebellum.[28] Messenger RNA of trkC is also found in the ventral mesencephalon[18] and in motoneurons.[21] Like trkB, there are truncated and therefore presumably nonsignaling forms of trkC.[6]

Neurotrophin 4/5 is the most recently discovered member of the neurotrophin gene family. Cells in the peripheral nervous system that are responsive to NT-4/5 include trigeminal, dorsal root ganglion, jugular, sympathetic, and nodose ganglion neurons.[17,29] In the central nervous system, hippocampal neurons and dopaminergic and GABAergic neurons of the ventral mesencephalon respond,[18,26] as do motoneurons.[21] Messenger RNA of NT-4/5 is found in muscle and other peripheral tissues[16] and in the central nervous system. The highest amounts in the central nervous system were found in pons or medulla, hypothalamus, thalamus, and cerebellum.[24] Neurotrophin 4/5 is known to activate the trkB receptor (Figure 1).

The discovery of NGF as a target-derived trophic factor for peripheral neurons has had a major influence on studies directed at understanding its expression and actions in both the peripheral and central nervous systems. In general, data for the expression of NGF and trkA indicate that NGF produced in the target of developing and mature neurons acts through trkA to maintain the survival and enhance the differentiation of responsive neurons. The situation may be more complex for the other neurotrophins. In some instances, a target-derived trophic relationship can be inferred. In others, it appears that autocrine or paracrine relationships may hold. An example of the latter is found in the hippocampus, where it has been shown that certain hippocampal neurons contain mRNA of both BDNF and trkB.[24] A further complication is the production of truncated versions of both trkB and trkC. It will be interesting to further define and characterize the trophic relationships that neurotrophins use to influence the survival and function of their responsive cells.

Ciliary Neurotrophic Factor

During the past few years exciting developments have occurred with respect to another neurotrophic factor called ciliary neurotrophic factor (CNTF). This factor was first purified as a substance extracted from intraocular tissues that supported the survival of ciliary ganglion neurons.[30] In its activity on ciliary neurons and by physicochemical characteristics, the partially purified factor was found to be distinct from NGF. An enriched source of CNTF was found in the adult rat sciatic nerve, and a modified purification protocol was used to purify CNTF activity from this source.[30] This allowed sequencing studies to be done, and eventually CNTF was cloned in several laboratories.[31-33] As predicted from the complementary DNA (cDNA) sequences in rats, rabbits, and humans, CNTF is a protein of 200 amino acids with a molecular weight of 22,700. The availability of purified recombinant protein considerably enhanced studies of the biologic activity of CNTF. Responsive cells of the peripheral nervous system include ciliary ganglion neurons, dorsal root ganglia neurons, sympathetic neurons, and adrenal chromaffin cells. In the central nervous system, hippocampal neurons, forebrain cholinergic neurons, and other populations, including spinal cord motoneurons, are responsive.[17,30] The survival of motoneurons is enhanced by CNTF both in vitro and in vivo.[34-36] In recent studies, disruption of the CNTF gene was shown to produce progressive atrophy and loss of motoneurons.[37] Interestingly, oligodendroglial progenitor cells, referred to as 02A cells, respond to CNTF, as do mature oligodendrocytes.[38]

As indicated, peripheral nerves serve as a rich source for CNTF. The production of CNTF in Schwann cells explains the levels present.[30] An interesting feature of CNTF is the absence of a signal sequence. The meaning of this finding is uncertain, but the suggestion has been made that CNTF release may normally require cell injury with membrane disruption. Ciliary neurotrophic factor-like activity can be shown in stumps affixed to a lesioned nerve in the first few days after a nerve lesion.[30] In the central nervous system astrocytes may produce CNTF,[39] and the levels of production may increase after injury. Thus, it has been suggested that CNTF may play the role of a lesion factor.[30]

The actions of this neurotrophic factor include enhanced neuronal survival. This has been most dramatically demonstrated in studies in vivo. Axotomy of the facial nerve of newborn rats normally results in a substan-

tial loss of motoneurons in the facial nucleus. The application of CNTF to the proximal stump prevented the loss of most neurons.[35] Ciliary neurotrophic factor enhances the cholinergic differentiation of neonatal sympathetic neurons, an effect that parallels the actions of another neurotrophic factor called leukemia inhibitory factor (LIF).[30] These two factors are biochemically distinct, but activate similar receptors (discussed later). An interesting feature of CNTF action in the central nervous system is its ability to prevent the death of axotomized medial septal neurons, both cholinergic and noncholinergic in type. Interestingly, although CNTF promoted the survival of cholinergic neurons that are marked by $p75^{NGFR}$, it did not maintain the activity of choline acetyltransferase, its neurotransmitter synthetic enzyme.[30]

Experiments to identify the CNTF receptor led to the discovery that a specific CNTF binding protein, designated CNTF receptor α (CNTFRα), was homologous to a receptor for the hematopoietic cytokine, interleukin-6 (IL-6).[40] This finding led to several developments. The first was a structural analysis that suggested that IL-6 and CNTF were themselves distantly related and members of a larger family of cytokines that includes LIF, granulocyte colony-stimulating factor, and oncostatin M. All of these factors were known to activate similar intracellular signaling events, and there was the possibility that they used similar receptor systems. Subsequently it was found that CNTF, IL-6, LIF, and oncostatin M do share signal transducing receptor components (Figure 2).[40] All of them use gp130, a transmembrane protein initially identified as the IL-6 signal transducer. In addition, CNTF, LIF, and oncostatin M require a second signal transducer known as LIFRβ. Specificity of CNTF actions arises from its binding to the α-receptor component, together with LIFRβ and gp130. Receptor activation arises from the formation of a heterodimer between LIFRβ and gp130 (Figure 2). The signal is transduced through the activation of a family of cytoplasmic tyrosine kinases known as the Jak-Tyk family. Activation of these kinases leads to the initiation of the signaling cascade in the responsive cell, which includes the phosphorylation of other cellular proteins.[41] One of these is called acute-phase response factor. Acute-phase response factor is a latent cytoplasmic transcription factor that is rapidly activated in response to CNTF.[42]

Distribution of the CNTFRα receptor should define possible sites of CNTF action. In fact, through in situ hybridization histochemistry, CNTFRα has been localized to all the known neuronal targets of CNTF, including neurons in the peripheral ganglia and spinal cord motoneurons.[40] An interesting possibility arises from the structure of CNTFRα. This is a glycosylphosphatidylinositol-linked protein. This linkage is susceptible to enzymatic cleavage, and soluble CNTFRα can be found in cerebrospinal fluid.[40] It is known that cells bearing gp130 and LIFRβ that are normally not responsive to CNTF can be induced to respond by adding CNTF with soluble

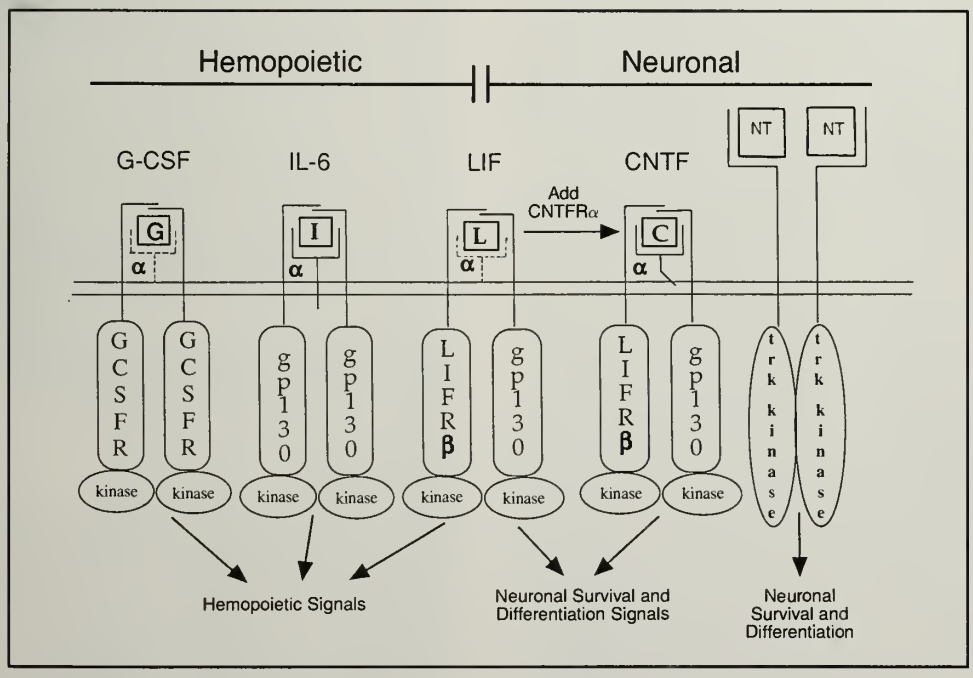

Figure 2.—Models are shown of granulocyte colony-stimulating factor (**G-CSF [G]**), interleukin-6 (**IL-6 [I]**), leukemia inhibitory factor (**LIF [L]**), and ciliary neurotrophic factor (**CNTF [C]**) receptor complexes (GCSFR, gp130, LIFRβ, and CNTFRα) compared with the trk receptor tyrosine kinases used by neurotrophins (**NT**) (adapted from Ip and Yancopoulos[40]). The cytokine receptors are depicted as either homodimers or heterodimers of β (gp130 and LIFRβ) components. Complex formation, including the dimerization of β-subunits, only occurs in response to ligand, and results in activation of associated Jak-Tyk tyrosine kinases. In the model, CNTFRα converts a functional LIF receptor complex into a functional CNTF receptor complex. Possible α components for G-CSF and LIF receptor complexes are indicated by dashed lines.

CNTFRα.[43] This suggests two possibilities. First, following the release of CNTFRα from the neuronal membrane, it could act to bind CNTF and prevent it from binding to its receptor on neurons. Alternatively, after binding to CNTF, CNTFRα could carry it to cells expressing gp130 and LIFRβ and induce a response. This analysis suggests a complexity and spectrum of CNTF actions that may be different from those of the neurotrophins.

Other Growth Factors of Interest

The insulin gene family comprises the genes for insulin and the insulinlike growth factors I and II (IGF-I and IGF-II). There is increasing interest in the actions of these molecules in the nervous system. Insulinlike growth factor I is of considerable interest. The mRNA for IGF-I is present in the target zones of trigeminal and sympathetic neurons during the innervation period. It is also found in projection neurons in the maturing sensory and cerebellar relay systems and in nonpyramidal cells of the hippocampus and cerebral cortex. It may also be synthesized by Purkinje cells in the developing cerebellum.[44] There is regulation of IGF-I mRNA levels during development with differences from region to region in the brain. Support for an IGF-I role in developmental regulation of neuronal function and survival comes from in vitro studies showing that IGF-I can induce neurite outgrowth in cultured motor, sensory, and sympathetic neurons. In addition, cortical neurons have been shown to respond, and IGF-I induces oligodendrocyte differentiation and myelin synthesis.[44] Suggesting a role for IGF-I in the development of the neuromuscular junction, IGF-I mRNA levels increase in muscle between embryonic day 14 and birth. Postnatal inhibition of IGF-I mRNA may contribute to the elimination of polyneuronal innervation.[45]

Insulin and the IGFs elicit their actions by binding to specific receptors on the surface of responsive cells. The receptors for insulin and IGF-I are similar.[44] Each is a disulfide-linked heterotetramer consisting of two α- and two β-subunits. The two α-subunits bind the ligand through a cystein-rich domain. These subunits lie entirely outside the cell. The β-subunits, which are linked by disulfide bridges to the α-subunits, contain a short extracellular domain and a transmembrane segment, followed by a cytoplasmic domain. The cytoplasmic domain contains an adenosine triphosphate-binding site and a tyrosine kinase domain. These receptors are formally similar to those defined earlier for the neurotrophins. Activation of the receptor occurs through ligand binding to the α-subunit with a subsequent conformational change in the β-subunits leading to receptor tyrosine kinase activation and autophosphorylation. This is followed by the activation of various intracellular substrates through phosphorylation and the initiation of a cascade of events leading to the biologic response. The IGF-II receptor is distinct from that for insulin and IGF-I. The IGF-II receptor is a single polypeptide chain with a large extracellular domain and a short cytoplasmic domain. Signaling through this receptor may involve glycine protein activation. The concentration of IGF-I receptors peaks in the brain during fetal development. Examining the postnatal and mature brain, IGF-I receptor mRNA is found in sensory and cerebellar relay systems, in the frontal cortex, Ammon's horn, the amygdaloid nuclei, and the suprachiasmatic nucleus. Autoradiography for IGF-I receptors shows rather dense labeling in the olfactory bulb, cerebellum, choroid plexus, and other sites including neocortex.[44] Thus, both IGF-I and its receptor are widely distributed.

Recently a glial cell line-derived neurotrophic factor (GDNF) for midbrain dopaminergic neurons has been described.[46] This potent factor was secreted by a rat glial cell line. It was purified to homogeneity and shown to promote dopamine uptake in cultures of neurons from the midbrain. Both rat and human cDNA for GDNF were cloned using probes based on the amino terminal sequence of purified GDNF. The protein predicted from the sequence data is a secreted molecule of 134 amino acids. It apparently exists as a disulfide-bonded homodimer and is distantly related to members of the transforming growth factor-β superfamily. In midbrain cultures, GDNF promoted the survival and differentiation of dopaminergic neurons. These effects appeared to be relatively specific in that GDNF did not act on GABAergic or on serotonergic neurons.[46]

Animal Models of Disease Treated by Neurotrophic Factors

The remarkable ability of neurotrophic factors to stimulate the survival and differentiation of neurons has suggested their use as trophic agents in diseases. Given advances in understanding the actions of these factors and the distribution of their receptors, we can now begin to develop a list of neurologic disorders and a corresponding list of factors that may prove useful (Table 2). Important diseases that might respond to neurotrophic factors are Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Peripheral neuropathy also suggests itself. Clinical trials are currently underway for amyotrophic lateral sclerosis and vincristine-induced peripheral neuropathy. At the same time, ongoing experiments in animal models of disease encourage the view that neurotrophic factors can be used to treat neurologic disorders.

Nerve Growth Factor Treatment of Taxol Neuropathy

Interesting studies have been done on NGF effects on the toxic neuropathy produced by the chemotherapeutic agent taxol.[47] Taxol has been used against solid tumors such as malignant melanoma and ovarian carcinoma. Unfortunately, its use induces a toxic sensory neuropathy, and this phenomenon has limited its clinical usefulness. The effects of NGF on sensory neurons both in vivo and in vitro encouraged a study in which this trophic factor was used to attempt to prevent taxol neuropathy in vivo.

For these studies an animal model for taxol neuropathy in mice was established. Taxol was administered to the mice intraperitoneally for six days, and they were tested three days thereafter for changes in sensory function. To assess thermal pain threshold, a modification of a

TABLE 2.—*Neurologic Disorders and Candidate Neurotrophic Factors for Therapy*

Disorder	*Neurotrophic Factor**
Peripheral neuropathy	
Sensory neurons	NGF, BDNF, NT-3, NT-4/5
Sympathetic neurons	NGF, FGF-2
Parasympathetic neurons	CNTF
Amyotrophic lateral sclerosis	
Motoneurons	CNTF, BDNF, NT-4/5, IGF-1
Alzheimer's disease	
Basal forebrain cholinergic neurons	NGF
Neocortical neurons	BDNF, NT-3, NT-4/5
Hippocampal neurons	BDNF, NT-3, NT-4/5
Parkinson's disease	
Dopaminergic neurons	GDNF, BDNF, NT-4/5, FGF-1, FGF-2, IGF-I
Huntington's disease	
Striatal interneurons	BDNF, NT-4/5
Striatal cholinergic neurons	NGF

*See Table 1 for abbreviations of neurotrophic factors.

standard tail-flick test was used. Mice were partially restrained, and their tails were placed in a beaker of water. The temperature of the water was increased in increments, and the experimenters observed the temperature at which the mouse flicked its tail out of the water. They were able to show that taxol significantly increased the temperature at which tail-flick occurred. When NGF was administered with taxol, there was no significant difference from control animals in tail-flick temperature. Administering taxol was also found to reduce the mean level of substance P in the dorsal root ganglia. Substance P marks a portion of the NGF responsive neurons in the ganglia. Remarkably, NGF prevented the taxol-mediated decrease in substance P levels. Electrophysiologic studies were also carried out, and compound sensory amplitudes were depressed in the taxol-treated subjects. The coadministration of NGF prevented the decrease. There was little if any effect of taxol on the distal latency recorded in the caudal nerve.[47]

These studies demonstrate clearly that NGF can prevent the effects of taxol on measures of sensory nociceptive function. How NGF exerts its effects is uncertain. One possibility is that it in some way directly counteracts taxol's effects. Another possibility is that NGF protects neurons through some indirect means. An interesting possibility raised by investigators is that taxol's effects on the cytoskeleton may in some way inhibit retrograde transport of the signal normally arising from NGF binding to its receptors in the periphery of sensory neurons.[47] If this were the case, then the administration of exogenous nerve growth factor could correct this deficiency by binding to receptors on or near the cell body. These studies suggest that NGF may be used to limit the dose-related toxicity of taxol and thus to facilitate the use of this drug in cancer patients. Conceivably, NGF or other neurotrophic factors acting on peripheral neurons could be used to augment the clinical usefulness of other cancer chemotherapeutic agents that produce peripheral nerve injury.

Ciliary Neurotrophic Factor and Motoneuron Disease

Several mouse mutants have been used to model motoneuron disease. The pmn/pmn mouse is an autosomal recessive mutant with progressive motor neuronopathy.[48] In homozygotes, paralysis of the hind limbs begins during the third week of life. The forelimbs become weak thereafter, and all mice die between six and seven weeks following birth. Histologic study of muscle shows neurogenic atrophy. Axonal degeneration is seen, which appears to start at motor end plates; it is found predominantly in sciatic nerve and its branches and in the phrenic nerve. Unaffected nerve fibers are normally myelinated, and sensory axons are spared. In the ventral horns, motoneurons show a reduction in cell size, then chromatolysis, and finally cell death. The gene responsible for this disorder is unknown.

On the basis of CNTF effects on motoneurons in vivo and in vitro, including the ability of this factor to prevent lesion-mediated degeneration of rat motoneurons during early postnatal life,[35] investigators pursued the hypothesis that CNTF could be used to prevent motoneuron degeneration in pmn/pmn mice.[49] It was first demonstrated that abnormalities in CNTF production were unlikely to cause the disease. Messenger RNA levels of CNTF in the sciatic nerve of these subjects were similar to those in normal mice. Also, extracts of nerves showed an equivalent amount of CNTF biologic activity. To administer CNTF to these subjects, a stable cell line was created by a transfection of mouse D3 cells with a construct in which CNTF genomic DNA was cloned 3′ to a cDNA fragment coding for the first 20 amino acids of the mouse prepro/NGF sequence, which includes the entire signal peptide for this molecule. The thought was that this construct would allow both synthesis and secretion of CNTF in these animals. Experiments in which CNTF expression was tested in vitro showed that CNTF activity was readily released into the culture medium. After intraperitoneal

administration of these cells on postnatal day 21, intraabdominal tumors were produced, and it was shown that CNTF was released into the serum of these animals. The production of CNTF in vivo was associated with enhanced survival and with enhanced motor performance compared with untreated or mock-treated pmn/pmn mice. Both treated and untreated mice were killed between postnatal days 40 and 48. Examination of the facial nucleus showed that the number of motoneurons was greatly decreased in pmn/pmn mice and that treatment with CNTF had a large protective effect. Thus, whereas in untreated mice only 60% of neurons remained, in treated mice, 86% of cells were present. Also, the number of axons in the phrenic nerve was substantially increased by CNTF treatment.[49]

The data show that CNTF rescues motoneurons from degeneration in pmn/pmn mice. They suggest that CNTF might be used to prevent motoneuron death and dysfunction in motoneuron disease in humans. The possibility is raised that other factors active on motoneurons might also be useful, either given separately or in conjunction with CNTF.

Nerve Growth Factor and the Trisomy 16 Mouse

The focus of work in our laboratory has been on understanding the natural processes of normal and diseased basal forebrain cholinergic neurons. Special emphasis has been placed on the response of these neurons to neurotrophic factors, especially NGF. Basal forebrain cholinergic neurons atrophy and die in patients with Alzheimer's disease, and it is known that these neurons are likely to contribute substantially to learning and memory deficits in these patients.[50] In developing an animal model for Alzheimer's disease, we made note of the interesting observation that the neurologic abnormalities of Alzheimer's disease universally develop at an early age in patients with the Down syndrome (trisomy 21). We reasoned that an animal model for Down syndrome might recapitulate important features of the neuropathogenesis of Alzheimer's disease and allow us to pursue the mechanism for the degeneration of basal forebrain cholinergic neurons. The trisomy 16 mouse is a genetic model for human Down syndrome. Mouse chromosome 16 contains a cluster of genes and loci that are also located on the proximal arm of human chromosome 21. These include the amyloid precursor protein, one of the glutamate receptor genes, and superoxide dismutase 1. Fetal trisomy 16 mice demonstrate phenotypic features seen in Down syndrome, including endocardial cushion defects and hematologic and immunologic abnormalities.

We hypothesized that cholinergic neurons of trisomy 16 murine basal forebrain would show degenerative changes over time in vivo. To compare cholinergic neurons from trisomy 16 and from normal mice, we transplanted fetal basal forebrain from trisomy 16 mice and from control fetuses into the hippocampus of normal mice. The hippocampus is the normal target of these neurons. Transplantation experiments showed that both trisomy 16 and control grafts survived for long periods in vivo. Interestingly, while cholinergic neurons appeared normal in both trisomy 16 and control transplants after one month, after six months there was clear-cut atrophy of trisomy 16 neurons. Atrophy was specific for cholinergic neurons.[51] To determine whether NGF could reverse this atrophy, NGF was administered by intraventricular cannulae between 5½ and 6 months of age. Vehicle injection served as the control. Animals were killed at 6 months of age, and grafts were assessed by immunostaining for choline acetyltransferase, the neurotransmitter synthetic enzyme for cholinergic neurons. As in earlier studies, there was atrophy of trisomy 16 cholinergic neurons relative to control neurons. The mean cross-sectional area was reduced by about 20% in vehicle-treated subjects. Following NGF infusion, trisomy 16 cholinergic neurons were significantly enlarged. Remarkably, both trisomy 16 and control neurons treated with NGF were substantially larger than control cholinergic neurons in vehicle-treated animals. The increase for trisomy 16 cells was to a size 29% greater than vehicle-treated control cholinergic neurons. There was no significant difference between the size of NGF-treated trisomy 16 and control neurons.[52] In follow-up studies we asked whether NGF levels were different in the hippocampus of animals that received trisomy 16 cells versus those that received control cells. No difference in NGF levels was apparent. Indeed, the size of the host basal forebrain cholinergic neurons, which have their axons in the same hippocampal territories as transplanted cells, was normal on both the side of the trisomy 16 transplant and the side of the control transplant. This suggests that the level of NGF available to trisomy 16 and control neurons was equivalent. We next asked whether NGF receptors continued to be expressed in neurons of trisomy 16 mice. We found evidence of both trkA and $p75^{NGFR}$ expression in both control and trisomy 16 neurons.[52] The levels of receptor expression and binding are now being addressed.

Using the trisomy 16 mouse model of the Down syndrome, we have shown that NGF can reverse genetically determined neuronal atrophy. Further analysis of this model may give insight into pathways that lead to neuronal degeneration in vivo and establish how NGF and other neurotrophic factors could be used to prevent dysfunction and death of these neurons in Alzheimer's disease.

Pursuing the Mechanisms of Neurodegeneration

The studies cited in this article give evidence that neurotrophic factors can prevent or reverse the degeneration and dysfunction of neurons caused by environmental and genetic insults. In addition to suggesting novel forms of therapy for these disorders, they raise the question of whether neurotrophic factors may be implicated in the pathogenesis of nervous system disorders. One possibility is that a primary deficiency of the neurotrophic factor is at the root of the disease. The examples cited earlier provide evidence that this is not required to produce such disorders. Indeed, in the case of the trisomy 16 mouse

transplants, atrophy occurred over a several-month period in vivo in the presence of what appear to have been normal levels of NGF. Thus, it would appear that an intrinsic abnormality in trisomy 16 cells was responsible for the changes that were demonstrated. No abnormality of a trophic factor has yet been clearly implicated in a disease state. Nevertheless, recent exciting work on mice in which the genes for either NGF or BDNF have been knocked out show unequivocally that eliminating the production of individual neurotrophic factors can produce considerable neuronal loss.[53,54]

A second possible explanation for neurodegeneration is that there is some fundamental abnormality in the receptor for a specific neurotrophic factor. Again, there are no disease examples to prove the case, but the possibility can be easily envisioned. A third possibility is that events downstream from the receptor that are important for signaling that leads to a maintenance of neuronal survival and function are altered in diseased neurons. In fact, these two possibilities can be combined in the case of the trisomy 16 mouse to suggest a means by which these neurons degenerate. It is known that NGF must bind to these receptors to activate its responsive cells. It is known also that one response to NGF is for gene expression for its receptors to be induced in these neurons.[55] Thus, even a subtle decrease in the ability of NGF receptors to be bound or activated by NGF, or in any of the many downstream events leading to the regulation of receptor gene expression, could in time result in fewer receptors at the cell surface. This situation could create progressive neuronal atrophy and conceivably even death of these cells in the presence of normal levels of NGF.

Finally, it is worth mentioning that the response of neurons to neurotrophic factors could be substantially different in patients with disease. The possibility can be envisioned that both beneficial and deleterious effects could arise from neurotrophic factor treatment of diseased neurons. Although it will be difficult to predict in advance in which diseases this may occur, these observations argue strongly for carrying out studies in realistic animal models of disease before human trials are conducted. In the case of the trisomy 16 mouse, NGF treatment did not appear to injure the responding neurons and created no new disorder.[52] Thus, for NGF there is no evidence that a deleterious effect would accompany its actions on diseased basal forebrain cholinergic neurons.

The observations cited in this article make it clear that there is a great deal of work yet to do to understand and to exploit the therapeutic potential of neurotrophic factors. Studies on the biology of these factors must proceed concurrently with studies designed to understand the mechanism of their action in reversing neurodegeneration.

Clinical Trials Using Neurotrophic Factors

There are several ongoing trials in which neurotrophic factors are being used to attempt to inhibit the dysfunction and death of neurons in specific neurologic disorders. Genentech has sponsored studies examining NGF for the treatment of peripheral neuropathy. A Phase I trial is now complete, and there are plans for testing NGF effects in diabetic neuropathy later this year. Genentech has also announced an interest in sponsoring trials of NGF in Alzheimer's disease. The neurotrophic factor would be delivered by intraventricular cannula. This ambitious trial is scheduled to begin within the next year. Amgen-Regeneron Partners are sponsoring a project to examine the effects of BDNF in amyotrophic lateral sclerosis. Other trials of neurotrophic factors have also been directed at this neurologic disorder. A Regeneron-sponsored Phase III trial using CNTF at either a high or a low dose was recently completed. The final analysis of the data is pending, but based on an interim analysis, it is not expected that CNTF-treated patients will be improved relative to placebo-treated controls. This is thought to be due, at least in part, to impaired neuromuscular function resulting from untoward side effects, which included anorexia, weight loss, nausea, and cough. A second trial for CNTF in amyotrophic lateral sclerosis is being sponsored by Synergen. In this trial, CNTF is being used at a lower dose. There are no results as yet available. Cephalon is also sponsoring trials in this disorder, using IGF-I in a Phase II/III North American trial that should be completed by the end of 1994. Preliminary data analysis is expected to be available in early 1995. Cephalon is sponsoring a similar trial in Europe; preliminary data should be available by mid- to late-1995. Finally, Cephalon is planning a Phase II trial using IGF-I in vincristine neuropathy.

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Selective Targeting of the Immune Response in Autoimmune Demyelination

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Recent developments in molecular and cellular immunology have led to the formulation of refined models that describe how tolerance to self-antigens is broken and autoimmunity develops. This knowledge can now be used to develop alternative approaches to conventional immunosuppression for the treatment of autoimmune demyelinating disorders. The ideal therapy would reverse established disease or prevent further progression by selectively eliminating the aggressive effector molecules or cells while leaving the immune system virtually intact. Indeed, several groups are engaged in preliminary or advanced clinical studies of promising specific immunotherapies for multiple sclerosis and other autoimmune conditions. Current data suggest that the immune response that results in organ-specific autoimmunity is highly complex and redundant in humans. This suggests that antigen-specific approaches may be less successful than broader immunotherapeutic strategies for treating multiple sclerosis and related diseases.

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Among human demyelinating diseases of the central nervous system, the most common is multiple sclerosis. Numerous laboratory, epidemiologic, and family studies suggest that tissue injury in multiple sclerosis results from aberrant immune reactivity to one or more myelin antigens. This injury is triggered in genetically susceptible persons by an environmental exposure to an as-yet-undefined causal agent (presumably a virus). The autoimmune model of multiple sclerosis pathogenesis has set the tone for immunotherapy in this disease, first by general immunosuppression using cytotoxic drugs and more recently by selectively targeting a specific branch of the immune response.

Autoimmune diseases are characterized by a breakdown in the mechanisms mediating tolerance to autoantigens. Consequently, a person's immune system is triggered to mount a pathologic response against that person's components. This response can be generalized in diseases like systemic lupus erythematosus or targeted to a particular compartment or organ as in multiple sclerosis, myasthenia gravis, Graves' disease, or rheumatoid arthritis. Our current view of disease mechanisms has been enhanced by the cloning and sequencing of autoantigens, the structural analysis of the major histocompatibility complex (MHC) gene products, the genetic analysis of the T-cell antigen receptor (TCR), and our understanding of cytokine function. In addition, we have learned a great deal from animal models of experimental T cell-mediated demyelination, in particular experimental allergic encephalomyelitis (EAE) in rodents and nonhuman primates. Experimental allergic encephalomyelitis is created by immunizing genetically susceptible animals with myelin antigens, producing an immune response against central nervous system white matter that results in acute or chronic disease. Many therapeutic approaches that have been successful against EAE are in trial for multiple sclerosis. As a result of transgenic and targeted mutagenesis technologies, novel animal models are now available, each uniquely expressing or missing a defined protein in a given tissue. These models have contributed substantially to our current view of how T-cell unresponsiveness to autoantigens is maintained.

During T-cell ontogeny in the thymus, lymphoid stem cells undergo differentiation during consecutive waves of thymic selection.[1,2] Thymocytes that will be useful to the host undergo positive selection, while thymocytes with autoreactive potential undergo negative selection by clonal deletion or inactivation. The "affinity or avidity" model may explain the balance between negative and positive selection.[3] This hypothesis suggests that only cells bearing receptors with an intermediate affinity or avidity toward a person's own MHC-peptides complexes would survive selection. Those with lower avidity would fail to be positively selected, whereas those with high affinity or avidity would be negatively selected. Thymic regulation is extended to the periphery in the form of clonal anergy or idiotypic interactions.[4,5] It is not completely clear why some of these cells escape this surveillance and later in

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ABBREVIATIONS USED IN TEXT

CTL = cytotoxic T-cell line
EAE = experimental allergic encephalomyelitis
IFN-β = interferon beta
IFN-γ = interferon gamma
IL = interleukin
MHC = major histocompatibility complex
TCR = T-cell [antigen] receptor
TNF = tumor necrosis factor

life participate in autoimmune pathogenic processes, but the many events that are required to induce self-reactivity may include tissue damage by trauma or infection and genetically determined susceptibility.

T cells recognize their ligand, a peptide product of the antigen degradation process, through the heterodimer α/β (or γ/δ) antigen receptor in the framework of MHC molecules expressed in the membrane of antigen-presenting cells. The trimolecular complex, MHC-peptide-TCR, is the focal point for the initiation and propagation of most immune responses to protein antigens, including self-antigens. Consequently, components of this complex are attractive candidates to target for immunomodulation. Indeed, much of the literature on immunotherapy for experimental autoimmunity describes attempts to specifically block the MHC-peptide-TCR interaction or, by extension, to block coreceptors, such as CD4, CD8, and B7, or adhesion molecules such as very-late-antigen 4, leukocyte functional antigen type 1, and intercellular adhesion molecule type 1. Several extensive reviews have examined T cell-antigen recognition as the target for immune intervention.[6-9] Readers are referred to these texts. In this article I will examine some recent experimental data that might advance the discussion of the feasibility of identifying alternative strategies for selective immune intervention.

Antigen Peptide Therapy

Using single amino acid substitutions in the TCR contact sites of synthetic peptides that represent epitope stretches of putative autoantigens, it is possible to design analogues that maintain their binding capacity to the MHC molecule, but stimulate the responding T cells in a unique way. Depending on the experimental system, some analogues will behave as antagonists by blocking the signal to T cells, while others may act as agonists by triggering a different type of response that is elicited by the wild-type pathogenic ligand.[10,11] Thus, "designed" synthetic peptides can have regulatory effects on the immune response and may open new possibilities of specific intervention. But because antagonists will probably interact with particular α/β TCR heterodimers, it is not clear how effective they might be in a heterogeneous in vivo response. Although there are no examples of successful applications of peptide-based therapies in humans, the continuing advances in the analysis of naturally MHC-bound antigen peptides provide a strong argument for further studies in the field. It has been recently reported that in nature, some viruses may use a similar strategy to inhibit the immune response. Naturally occurring human immunodeficiency virus type 1 glycosaminoglycan variants induce in vitro antagonism of cytotoxic T-cell lines (CTL).[12] This effect was experimentally demonstrated using synthetic peptides as epitopes, or cell-processed full-length proteins expressed by either recombinant vaccinia constructs or replicating the human immunodeficiency virus. Furthermore, natural antagonism by variant epitopes with the capacity to inhibit cytotoxic responses to the wild-type epitope seems to exist also in hepatitis B infection.[13] Cytotoxic T-cell line antagonism may represent a unique method of viral escape in vivo. Elucidating this mechanism may provide valuable information for the design of therapeutic synthetic antagonists and agonists to be used as immunomodulators.

Functional Diversity of T-Helper Cells

A variety of cytokines regulate the activation, differentiation, and proliferation of T lymphocytes. Under their influence, cells differentiate into two major pathways. Th1 cells produce interleukin (IL)-2, IL-3, tumor necrosis factor (TNF)-β, and interferon gamma (IFN-γ) and participate in inflammatory responses. Th2 cells produce IL-3, IL-4, IL-5, IL-10, and TNF-β. Recently a third subset of T cells, Th0, was identified, with a pattern of cytokine production overlapping that of both Th1 and Th2. In contrast to Th1 cells, Th2 cells do not depend on IL-2 for their autocrine growth and can proliferate to anti-CD3 in the absence of accessory cells.

It is widely accepted that the lack of second signals or costimulation provided by accessory cells causes mature T lymphocytes to enter a state of tolerance or anergy, where they fail to proliferate or produce lymphokines and are refractory to subsequent stimulation by antigen. It may be possible to selectively anergize the Th1 cells and enhance the modulatory Th2 response by introducing antigen without costimulation. For example, in vitro antigen stimulation in the presence of the soluble ligand CTLA4 will block the costimulation signal provided by B7.[14] Consequently, IL-2 and IFN-γ, but not IL-4 production, are inhibited, resulting in anergy of Th1 cells but stimulation of Th2 cells.

The oral administration of an autoantigen can also shift the cytokine balance and induce tolerance. The suppression of EAE with oral administration of myelin basic protein[15,16] provided preclinical support for trials with oral myelin in multiple sclerosis, oral collagen in rheumatoid arthritis, and oral S antigen in uveitis.[17] Recent experiments have elucidated the physiologic mechanisms underlying the induction of oral tolerance. Tolerance can be adoptively transferred by $CD8^+$ T cells that are generated following the oral administration of antigens and release transforming growth factor β after being triggered by the specific antigen. Transforming growth factor β suppresses immune responses in the microenvironment, creating a form of bystander suppression.[18] An alternative mechanism based on the induction of anergy to the autoaggressive T cells by the oral administration of a tolerogen was also proposed.[19]

A more direct approach to influence the cytokine network is to administer cytokines or, alternatively, cytokine receptor analogues or antagonists. The results of a multicenter, double-blind, placebo-controlled trial of interferon beta (IFN-β) given at two dosing schedules for three years to 372 patients with relapsing-remitting multiple sclerosis were recently published. Although substantial changes in disability could not be discerned, some efficacy was demonstrated. There was a reduction in the frequency and severity of relapses and a reduction in disease activity on magnetic resonance imaging.[20] The exact mechanism of action of IFN-β in multiple sclerosis treatment is unknown, but one effect may be to antagonize the stimulation of MHC molecules induced by IFN-γ. In this regard, it is of interest that a clinical trial of IFN-γ in multiple sclerosis resulted in an increase in the frequency of relapses.

Intracellular Targets

The binding of an antigen to its receptor ignites a complex signaling cascade that triggers the activation of downstream serine-threonine or tyrosine protein kinases. These signal-activated protein kinases will transmit the information generated at the receptor level to the transcriptional mechanism in the nucleus. This is achieved by a phosphorylation of transcription factors, or proteins that regulate transcription factors, resulting in changes in lymphocyte behavior and the expression of phenotypes. In the past few years, many of the intracellular events in the transduction signaling pathways have been elucidated, and key proteins have been identified.[21] This knowledge opens a new level of possible therapeutic intervention based on the design of drugs that can specifically modulate these pathways.[22] This approach is antigen-independent, but it can have a specific effect because it can affect the cells only if their antigen-specific receptor is engaged. Extraordinary developments in combinatorial chemistry provide the tools to test millions of compounds in a relatively short time, increasing the odds of finding such drugs.[23]

Superantigens

The term "superantigen" describes antigens that, at very low concentrations in the picomolar range, can selectively stimulate subsets of T lymphocytes.[24-26] Superantigens bind with high affinity to class II MHC molecules outside the antigen binding groove. They interact with the Vβ chain of the TCR in the region of the β-pleated sheet, away from the complementarity-determining CDR3 region, the putative antigen binding site. In a non-MHC-restricted manner, with no need for antigen processing, the class II-superantigen complexes trigger the proliferation of T cells expressing particular TCR-Vβ chains. This stimulation is independent of accessory molecules and induces the release of cytokines like IL-2, IFN-γ, and TNF. A notable feature of superantigenic stimulation is that responding T cells initially mount a vigorous response, but then disappear or display anergy.

Two groups of superantigens have been defined: endogenous[27,28]—retroviral sequences encoded within the genome that have been identified in the mouse, but not yet in humans—and exogenous. Exogenous superantigens include the toxins of many common bacteria and possibly components of certain viruses—for example, the nucleocapsid of the rabies virus.[29,30]

Superantigens are associated with numerous human diseases such as food poisoning, the toxic shock syndrome, the scalded skin syndrome, and others.[29-31] The involvement of exogenous superantigens as etiologic agents in several autoimmune diseases is now under investigation.[32,33] Infections may break clonal anergy of T cells that have possible autoreactive antigen receptors. For example, infection with the nematode *Nippostrongylus brasiliensis* breaks an established $CD4^+$ $V\beta8^+$ T-cell tolerance induced in mice.[34] Because many autoimmune diseases are exacerbated and maybe even preceded by infections, infectious agents may reverse the state of anergy on $CD4^+$ T cells tolerant to self-antigens, activating pathogenic pathways.[35]

Recently it was shown that relapses and exacerbations of EAE could be induced with the superantigen *Staphylococcus aureus* enterotoxin E and, to a lesser extent, *S aureus* enterotoxin A.[36] At least part of the observed effect is caused by a specific reactivation of autoreactive cells in the periphery and the production of TNF, because the administration of anti-TNF antibodies can substantially delay the onset of disease exacerbated by *S aureus* enterotoxin B. Interestingly, this superantigen can prevent disease when given at least 14 days before the expected onset of disease. Other investigators examined the ability of staphylococcal toxins to stimulate human T cells specific for myelin basic protein or proteolipid protein, putative autoantigens in multiple sclerosis.[37] All myelin antigen-specific T cells responded in proliferation studies to at least one of the nine superantigenic toxins used in this study. In some experiments, the superantigenic toxins were as much as 7×10^5 times more potent in proliferation assays than the myelin antigens to which the T cells were initially sensitized. The authors suggest the possibility that superantigenic massive stimulation during infection may be associated with the activation of myelin-specific T cells and disease exacerbation. These results may have therapeutic implications. In another study it was demonstrated that it is possible to inhibit superantigen recognition using peptides related to the site of interaction with the TCR in the variable region of the β-chain.[38]

The activation of T cells by superantigens requires the presence of class II MHC molecules or alternatively the cross-linking of toxin, or costimulants. In the absence of these conditions, superantigens such as *S aureus* enterotoxin B appear to cause anergy. Trace levels of superantigen suppress the pathogenic effect of encephalitogenic (EAE mediators) Vβ8-expressing T-cell clones.[39] It was recently observed that *S aureus* enterotoxin B can form biologically active complexes with soluble TCR molecules in both the absence and presence of class II MHC molecules.[40] This finding may provide an explanation for

TABLE 1.—*Experimental Strategies for Selective Immunosuppressive Therapy*

Monoclonal antibodies to
T-cell subpopulations (CD4)*
T-cell receptors†
Adhesion molecules†
Accessory molecules (CD40, CD80)‡
Class II MHC molecules‡
Cytokine receptors‡
Activation markers‡
Macrophages‡
Cytokines‡
T-cell vaccination*
TCR peptide vaccination*
Oral-induced tolerance*
Immunomodulation (Cop I*, linomide*)
Inhalation-induced tolerance‡
Cytokine receptor analogues and antagonists†
Cytokines—IFN-β,* TGF-β,† IL-4,‡ IL-10‡
Antigen peptides TCR analogues and antagonists‡
Blocking costimulation (anergy)‡
Class II MHC-peptides complexes‡
Anti-IgD peptide conjugates‡
Superantigen modulation‡
Metalloprotease inhibitors‡
Blocking-signal transduction pathways‡
Complement inhibitors‡
Regulation of MHC gene expression‡

IFN-β = interferon beta, IL = interleukin, MHC = major histocompatibility complex, TCR = T-cell receptor, TGF = transforming growth factor

*Clinical trials.
†Preclinical trial stage.
‡Experimental stage.

the anergic effect of superantigens in vivo in the absence of costimulants or cross-linking and may lead to new approaches for manipulating the immune response.

Conclusions

The concept of selective immunotherapy is based on the assumption that a specific effector mechanism (restricted T-cell repertoire, discrete antigenic epitope, defined cytokine pathway) can be identified at a specific stage of the autoreactive phenomenon. Whereas some studies suggest that a discrete repertoire of myelin basic protein-reactive T cells is important in the pathogenesis of multiple sclerosis,[41] T cells that react with other myelin proteins such as proteolipid protein, myelin oligodendrocyte glycoprotein, and myelin-associated glycoprotein, as well as other antigens like heat shock proteins, β-arrestin, and arrestin,[42-44] may play equally important roles in this disease. Specific immunotherapy for autoimmune demyelinating diseases using simple protocols of peptides or antibodies directed at single or multiple sites in the trimolecular complex is a formidable challenge. In established diseases, the pathologic immune response may involve multiple epitopes or even multiple antigens, and it is likely that a person's HLA background shapes the TCR repertoire. Consequently, immunotherapy will be combinatorial and customized to a certain extent. Other approaches not reviewed here include targeting molecules involved in lymphocyte homing and tissue destruction such as α4β1 integrin,[45] TNF-α,[46] zinc metalloendoproteases,[47] and others (Table 1). Many practical issues must be addressed—for example, the development of appropriate carriers to extend the half-life of peptides in vivo, or the design of antibodies that do not elicit anti-idiotypic responses. Beyond these practical concerns, basic questions remain unanswered. We need to learn more about genetic susceptibility and environmental influences on the development of autoimmunity.

The current understanding of the pathogenesis of multiple sclerosis and the molecular basis of antigen recognition and immune regulation provide the background and strategies for selectively intervening in autoimmune diseases of the nervous system. Results from some clinical trials, although encouraging, are inconclusive. The next major goal should be to identify the major genetic components involved in susceptibility to demyelination. Our hypothesis is that a primary genetic susceptibility triggers an autoreactive demyelinating phenomenon when a susceptible host is exposed to certain environmental factors or stresses. The characterization of these genetic influences will play a major role in defining the causes of autoimmune diseases and provide new perspectives for rational treatment.

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Gene Therapy for Diseases of the Nervous System

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Advances in molecular biology and recombinant DNA technologies have contributed to our understanding of the molecular basis of many diseases. Now the possibility of gene transfer into normal cells to produce a gene product of therapeutic potential, or into diseased cells to correct the pathologic alteration, promises to revolutionize medical practice. In contemporary medicine, many therapeutic strategies focus on the link between a biochemical deficiency and the ensuing disorder. The treatment of noninfectious disease is often based on replacement therapy; medication is given to compensate for biochemical defects and to prevent or reverse the progression of disease. Although conventional therapies seldom alter the fundamental cause of a disease, gene therapy potentially could correct, at a molecular level, the genetic abnormalities contributing to its pathogenesis. Treatment directed at specific molecular alterations associated with the development of neurologic disease provides expectations of more effective and less toxic therapy. The development of gene therapy for nervous system tumors has progressed rapidly and may be prototypical in the development of therapies for inherited and acquired disorders of the nervous system. We describe possible strategies for using gene therapy to treat nervous system disorders, and we review recent advances in gene therapy for nervous system tumors.

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Three decades ago, scientists developed techniques that enabled them to manipulate the genome of bacteria. Soon afterwards, advances permitted researchers to clone and then transfer genes into animal cells. It was during that time that progress in research laboratories fueled speculation that gene transfer might one day be used to treat disease in human patients. Gene transfer techniques have now established a foothold in modern clinical medicine,[1-8] and investigational gene therapy trials are under way for a variety of human diseases.[9-17]

Disease in the nervous system can have dire consequences for a stricken patient; those afflicted can be left immobile without sight, speech, or memory. This devastation occurs over the spectrum of neurologic disease, from the degenerative to the neoplastic forms. Distressingly, these particular diseases have defied modern therapeutics. For all of those reasons, gene therapy for disease of the nervous system has drawn the attention of researchers and clinicians alike.

Gene Therapy for Inherited Disease

The ideal design of a gene therapy strategy would first take into account the molecular basis of a disease process and then effectively tailor gene transfer techniques to mitigate toxicities and improve the effectiveness of existing therapies. A successful example of this strategy is provided by the efforts of investigators at the National Institutes of Health who developed a somatic cell gene therapy approach for the treatment of the severe combined immunodeficiency syndrome resulting from adenosine deaminase (ADA) deficiency.[4,10-13,17] Patients afflicted with ADA deficiency can be cured by matched bone marrow transplants providing immune cells with normal ADA levels. On that basis, it was proposed that the transfer of the human ADA gene into T lymphocytes from ADA-deficient patients might have the same effect.[4] An investigational approach was then designed in which mononuclear cells were isolated from the blood of patients with ADA deficiency, stimulated to proliferate in tissue culture, infected with a retroviral vector carrying the human ADA gene, and then returned to the patient.[10,12] Current reports of these patients' status indicate that this treatment approach may be efficacious.[17]

Key to the success of that strategy was the identification of a disease that resulted from a mutation in a single gene encoding an enzyme vital to the function of a recog-

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nizable class of cells. The isolation of T lymphocytes from a patient, the growth of those cells in tissue culture where conditions favoring efficient gene transfer could be maintained, and the return of cells expressing the desired gene back to the patient where they would resume their normal functions were all required for this strategy to succeed. Unfortunately, the use of this approach as a model of gene therapy for nervous system disease is, for many reasons, a formidable task.

Among currently recognized neurologic disorders, variations in the age of onset, the severity of disease at presentation, and the time course of disease progression suggest that the causes of disease may be multiple. It is also possible that several genetic alterations may contribute to a specific disease, and the effects of those changes may be independent of each other. Before effective gene therapy strategies can be designed to treat these diseases, the genes contributing to their development and the metabolic pathways mediated by the products of those genes will have to be better understood.

The challenge in the study of Huntington's disease is a case in point. Last year the Huntington's Disease Collaborative Research Group reported the cloning of a new gene, named *IT15*, from patients with this neurodegenerative disorder.[18] An expanded, unstable CAG trinucleotide repeat sequence was found in the 5′ coding region of the gene, and the length of the repeated sequence was found to correlate with the age of disease onset. Research is now focused on establishing the relationship between this trinucleotide repeat expansion, the function of the *IT15* gene, and the characteristic degeneration of neurons found only in the caudate and putamen in patients with Huntington's disease.[18] Treatment of the disease may have to address why neuronal degeneration occurs only in a particular location in the brain despite widespread expression of the protein encoded by the *IT15* gene. Although the neurons in the basal ganglia would be a logical target for gene therapy, gene transfer techniques cannot yet selectively target a class of neurons in a defined location; as specific cells in the nervous system have discrete functions, nonselective gene transfer could result in a certain class of cells gaining an inappropriate new characteristic that has adverse effects on their normal function.

Investigators pursuing approaches focused on developing new vectors for gene transfer to cells of the nervous system have turned to adenoviruses and neurotropic viruses, such as the herpes simplex virus.[19-23] In each case, it has been possible to show that foreign genes can be delivered to a variety of cell types in rodent brains, but advances in gene delivery techniques and knowledge about the mechanisms regulating the expression of transgenes in host tissue will be required before selected populations of cells in the nervous system can be targeted for gene therapy.

Somatic Cell Gene Therapy for Neurodegenerative Disease

Creative somatic cell therapies have been developed to circumvent the limitations of gene transfer into nervous system cells. These strategies have been used in experimental models, and they show promise for the management of some neurodegenerative diseases. Fibroblasts genetically modified to secrete nerve growth factor have been shown to prevent the death of cholinergic neurons when implanted into the brain after a surgical lesion was placed in the fimbria-fornix.[24] A pilot case in which nerve growth factor was infused into the lateral ventricle in a patient with Alzheimer's disease showed results that included increased cortical blood flow, normalization of electroencephalographic abnormalities, and improvement in some psychological tests.[25] These findings suggest that somatic cell approaches to gene therapy that lead to increased delivery of nerve growth factor may play an important role in therapeutic strategies designed to limit the loss of basal forebrain cholinergic neurons in patients with Alzheimer's disease.[26] A similar approach has been shown to be effective in reducing abnormal neurologic activity resulting from the destruction of nigrostriatal pathways in rodent models of Parkinson's disease after transplantation of cells modified to produce levodopa.[27]

Although these therapies do not address the mechanisms that initiate neurodegenerative disorders, they provide experimental evidence that the delivery of trophic factors and substrates by genetically modified somatic cells can alter disease progression and open new avenues for further clinical investigation. A gene therapy strategy modeled after the ADA protocol could play a role in delivering neuronal growth factors to the nervous system of patients with neurodegenerative disease. Cells from various tissues could be removed from a patient, be grown in tissue culture where they could be stimulated to replicate, be genetically modified with retroviral vectors carrying a gene of therapeutic importance, and then be implanted into a brain with the intent to increase the local delivery of biologically active molecules.[28,29]

Gene Therapy for Brain Tumors

The challenges that must be addressed in the design of gene therapy protocols for nervous system disease include the lack of knowledge about the genetic changes that lead to disease, the complexity of the structure and function of the nervous system, the limitations of effective techniques to deliver genes to the nervous system, and the possible toxicities of available vectors. For several reasons, these limitations have had less effect on the development of gene therapy strategies to treat tumors of the nervous system. First, most brain tumors are localized masses of proliferating cells surrounded by normal, postmitotic brain tissue; therefore, retroviral vector-mediated gene transfer can be selective for replicating tumor cells and can spare normal brain. Second, insertional mutagenesis is less of a concern when neoplastic cells are the target for gene transfer. A gene therapy strategy known as viral-directed enzyme prodrug therapy has used retroviral vectors to eliminate some types of experimental brain tumors in rodent models.[30-36] The basis of this approach is straightforward: a gene encoding an enzyme that converts an inactive prodrug into a therapeutically active metabo-

lite is transferred selectively into tumor cells. This enzyme can then mediate a cytotoxic effect in the infected cell. A key feature of this therapy is that retroviral vector-mediated gene transfer requires dividing cells,[37-39] and in the nervous system the most actively dividing cells are tumor cells.

To date, the most extensively studied strategy of viral-directed enzyme prodrug therapy for brain tumors has used a recombinant retrovirus vector into which the gene encoding the enzyme thymidine kinase from the herpes simplex virus *(HSVtk)* has been inserted. Following retroviral vector infection of a tumor cell, the *HSVtk* gene is incorporated into the host cell genome. The thymidine kinase of mammalian cells does not have a high affinity for certain nucleoside analogues, such as the antiviral drug ganciclovir, that the *HSVtk* enzyme will avidly phosphorylate. These phosphorylated analogues can be incorporated into the cellular genome during DNA replication, leading to tumor cell death. Because ganciclovir is not a substrate for the mammalian thymidine kinase, this drug does not harm normal cells when given in therapeutic doses.

The efficiency of retroviral-mediated gene transfer into tumor cells following the direct inoculation of retroviral vectors into intracerebral tumors in rodents is rarely greater than 1%. When xenografted tumors are injected with a murine fibroblast cell line producing recombinant retroviral vectors containing a marker gene, the percentage of tumor cells expressing the marker gene can be increased to 10%.[40] Although this suggests that only 10% of a tumor could be killed with ganciclovir therapy, it has been shown that, in some tumor models, cell death after infection with the *HSVtk*-containing retrovirus and treatment with ganciclovir far exceeds the number of cells that express the *HSVtk* gene. It has been shown that tumors in rodents could be eliminated after treatment with ganciclovir when as few as 10% of the cells expressed the *HSVtk* gene.[31] This is referred to as the "bystander effect," but the mechanism of this phenomenon is not known.[41-43] Evidence for the bystander effect has also been observed by several groups using the *HSVtk* and ganciclovir gene therapy strategy to treat a variety of tumor types in animal models.[44-48] To date, no evidence of toxicity to the normal brain in animals treated with this gene therapy strategy has been reported, and this suggests that the toxicity from the bystander effect is tumor-specific. Also, toxicity to organs outside the nervous system has not been detected, and no retroviral vector-induced secondary malignant neoplasms have occurred.[35]

When it is successful in animal models, the viral-directed enzyme prodrug therapy approach for treating experimental brain tumors appears to offer several possible advantages over the conventional therapies for brain tumors in human patients. The median survival of a patient with the most malignant type of glioma, glioblastoma multiforme, has remained at about a year over the past two decades, despite the development of treatment strategies that combine surgical therapy, irradiation, and chemotherapy.[49] For a patient with a newly diagnosed malignant glioma, the long-term prognosis is bleak because the natural history of this disease is one of unrelenting tumor growth with invasion of the surrounding brain that can be accompanied by symptoms of increased intracranial pressure and loss of neurologic function. Treatment is hampered by the invasive nature of this tumor, which makes it difficult to achieve a complete surgical resection and limits the radiation dose that can be used to treat residual tumor in infiltrated but normally functioning brain. The effectiveness of chemotherapy for patients who have brain tumors can be reduced by acquired drug resistance during therapy and the associated bone marrow suppression and organ toxicity. Also, reductions in the dose and frequency of drug administration may be required because of the age or medical condition of the patient. In contrast, retroviral-mediated gene transfer is selective for tumor cells in animal models, and there is no systemic toxicity associated with the administration of the prodrug ganciclovir. Although the bystander effect results in the death of a greater number of tumor cells than would be predicted by the number of cells that express the *HSVtk* gene, this toxicity appears to remain tumor-specific. Whether the success of this approach can be duplicated in human patients remains an open question.

Summary

In this review we have focused on the challenges of designing gene therapy protocols for the treatment of neurologic disease. An important goal of gene therapy will be to correct the phenotype of diseased tissue by altering the mutated genotype. Initially most gene therapy protocols may be designed to augment conventional therapies, as gene therapy could be most useful in conjunction with other therapies of proven efficacy. This will certainly be the case for the treatment of cancer of the nervous system as multimodality approaches predominate in current practice. Some gene therapy approaches may prove to be superior to standard therapy, whereas others may provide insights into mechanisms that could be exploited in the design of new therapies. The viral-directed enzyme prodrug gene therapy strategy has been shown to eliminate experimental brain tumors in animals. Although the mechanisms responsible for tumor cell death are not completely understood, this toxicity appears to be restricted to the tumor without effect on normal brain tissue. That capability has previously eluded researchers and suggests that knowledge regarding the molecular mechanisms that mediate both the pathogenesis of nervous system disease and the available therapeutic tools could provide key opportunities to devise more effective and less toxic therapies.

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Neurodegeneration in Humans Caused by Prions

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Prion diseases include kuru, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker disease, and fatal familial insomnia of humans as well as scrapie and bovine spongiform encephalopathy of animals. For many years, the prion diseases were thought to be caused by viruses despite evidence to the contrary. The unique characteristic common to all of these disorders, whether sporadic, dominantly inherited, or acquired by infection, is that they involve aberrant metabolism of the prion protein. In many cases, the cellular prion protein is converted into the scrapie variant by a process after translation that involves a conformational change. Often the human prion diseases are transmissible experimentally to animals, and all of the inherited prion diseases segregate with prion protein gene mutations.

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Investigations of neurodegeneration in humans and animals caused by prions have produced unexpected and striking findings. For many years, three uncommon human diseases and several animal disorders were labeled transmissible encephalopathies, spongiform encephalopathies, or slow virus diseases.[1-3] These illnesses are transmissible to experimental animals after a prolonged incubation period, and some features of the transmissible pathogen resemble those of viruses.[4-7] Yet early attempts to characterize the infectious pathogen causing scrapie in sheep and goats suggested that these transmissible agents differed from both viruses and viroids.[8,9]

A series of discoveries in the past three decades has led to the molecular and genetic characterization of the transmissible pathogen causing scrapie in animals and a quartet of human illnesses[10-15]: kuru, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker disease, and fatal familial insomnia. To distinguish this pathogen from viruses and viroids, the term "prion" was introduced to emphasize its proteinaceous and infectious nature.[16]

An abnormal isoform of the prion protein (PrP), known as the scrapie variant (PrP^{Sc}), is the only known component of the prion.[17,18] Prion protein is encoded by a gene on the short arm of chromosome 20 in humans.[19] The PrP^{Sc} variant differs physically from the normal, cellular isoform (PrP^{C}) by its high β-sheet content, insolubility in detergents, propensity to aggregate, and relative resistance to proteolysis.[20-22] While PrP^{Sc} is formed from PrP^{C} after the polypeptide chain is assembled,[23] attempts to identify a chemical modification that distinguishes the two PrP isoforms have been unsuccessful.[24] In contrast, biophysical studies have shown that PrP^{C} is rich in α-helices and is virtually devoid of β-sheet.[20] The conversion of PrP^{C} into PrP^{Sc} appears to involve the unfolding of α-helices and their refolding into β-sheets. Because infectious prions are composed largely, if not entirely, of PrP^{Sc}, this α-helix to β-sheet structural transition appears to be the fundamental event in the propagation of prions and the pathogenesis of neurodegeneration.

Clinical Manifestations of Prion Diseases

The human prion diseases are manifest as infectious, inherited, and sporadic disorders and are often referred to as kuru, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker disease, and fatal familial insomnia, depending on the clinical and neuropathologic findings (Table 1).

Kuru generally presented as an ataxic disorder, with the first manifestation of the disease being difficulty walking along steep mountain trails in the highlands of New Guinea. Most cases progressed steadily over a year to the point where, because of severe truncal ataxia, patients were no longer able to stand or sit without the aid of a pole implanted in the earth. In the terminal phases of the disease, they often manifested a dementia. With the cessation of ritualistic cannibalism about 40 years ago, kuru has almost disappeared.

Creutzfeldt-Jakob disease usually presents as a de-

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ABBREVIATIONS USED IN TEXT

CpG = phosphodiester bond of deoxycytosine and deoxyguanosine
PrP = prion protein
PrP^{C} = cellular variant of prion protein
PrP^{Sc} = scrapie variant of prion protein

menting illness in the sixth or seventh decade of life. In some cases the disease progresses rapidly, and the patients die within a few months. Most are dead within a year, but a few live as long as 15 years after diagnosis. About 10% of cases of Creutzfeldt-Jakob disease present with an ataxic syndrome that resembles kuru in many respects, but the dementia seems to appear much earlier.

Patients with the Gerstmann-Sträussler-Scheinker syndrome often present with ataxia; often they are initially given a diagnosis of multiple sclerosis and olivopontocerebellar degeneration. The clinical course of the disease can be unpredictable, with the duration varying from a year to two decades. Another form of the syndrome has been labeled "telencephalic Gerstmann-Sträussler-Scheinker," which presents with a dementia much like that of Creutzfeldt-Jakob disease.

The fourth human prion disease is fatal familial insomnia, which begins as an insomnia and autonomic nervous system dysfunction. Late in the course of the illness, which generally lasts about a year, signs of dementia appear.

Infectious forms of prion diseases result from the horizontal transmission of the infectious prions, as occurs in iatrogenic Creutzfeldt-Jakob disease and kuru. Inherited forms, notably Gerstmann-Sträussler-Scheinker disease, familial Creutzfeldt-Jakob disease, and fatal familial insomnia, make up 10% to 15% of all cases of prion disease. A mutation in the open reading frame or protein coding region of the *PRNP* gene has been found in all reported kindred with inherited human prion disease. Sporadic forms of prion disease comprise most cases of Creutzfeldt-Jakob disease and possibly some cases of Gerstmann-Sträussler-Scheinker syndrome.[25] How prions arise in patients with sporadic forms is unknown but has been hypothesized to involve horizontal transmission, somatic mutation of the open reading frame of the *PRNP* gene, and the spontaneous conversion of PrP^{C} into PrP^{Sc}.[2,26] Numerous attempts to establish an infectious link between sporadic Creutzfeldt-Jakob disease and a preexisting prion disease in animals or humans have been unrewarding.[27-29]

Diagnosis of Prion Diseases

A human prion disease should be considered in any patient who has a progressive subacute or chronic decline in cognitive or motor function. Being typically adults between 40 and 70 years of age, patients often have clinical features helpful in providing a premorbid diagnosis of prion disease, particularly sporadic Creutzfeldt-Jakob disease.[30] There is as yet no specific diagnostic test for prion disease in the cerebrospinal fluid. A definitive diagnosis

TABLE 1.—*Human Prion Diseases*

Disease	*Cause*
Kuru	Infection
Creutzfeldt-Jakob disease	
Iatrogenic	Infection
Sporadic	Unknown
Familial	Prion protein mutation
Gerstmann-Sträussler-Scheinker disease	Prion protein mutation
Fatal familial insomnia	Prion protein mutation

of human prion disease, which is invariably fatal, can usually be made from the examination of brain tissue. Over the past four years, knowledge of the molecular genetics of prion diseases has made it possible to diagnose inherited prion disease in living patients using DNA extracted from peripheral tissues.

The classic neuropathologic features of human prion disease include spongiform degeneration, gliosis, and neuronal loss in the absence of an inflammatory reaction. When present, amyloid plaques that stain with α-PrP antibodies are diagnostic. The presence of protease-resistant PrP (PrP^{Sc} or PrP^{CJD}) in the infectious and sporadic forms and most of the inherited forms of these diseases implicates prions in their pathogenesis.

The hallmark of all the prion diseases, whether sporadic, dominantly inherited, or acquired by infection, is that they involve aberrant metabolism of the prion protein.[10] Human prion disease can be rapidly and definitively diagnosed if PrP^{Sc} can be detected immunologically. In the familial forms of the prion diseases, molecular genetic analyses of PrP can be diagnostic and performed on DNA extracted from blood leukocytes after death. Unfortunately, such testing is of little value in the diagnosis of the sporadic or infectious forms of prion disease. In some patients with inherited prion disease, PrP^{Sc} is barely detectable or is undetectable,[31-34] a situation mimicked in transgenic mice, which express a mutant PrP gene and spontaneously develop neurologic illness indistinguishable from experimental murine scrapie.[35] Because molecular genetic analyses of *PRNP* genes in patients with unusual dementing illnesses are readily performed, the diagnosis of inherited prion disease can often be established where there was either little or no neurologic abnormality,[36] atypical neurodegenerative disease,[32] or misdiagnosed neurodegenerative diseases,[37] including Alzheimer's disease. Although the horizontal transmission of neurodegeneration to experimental hosts was for a time the "gold standard" of prion disease, it can no longer be used as such. Some investigators have reported that frequently inherited prion diseases from humans cannot be transmitted experimentally to animals (rodents) despite the presence of a pathogenic mutation in the *PRNP* gene.[7] Other investigators have been able to accomplish this using apes and monkeys as hosts.[38]

In summary, the diagnosis of prion or prion protein disease may be made in patients on the basis of the presence of PrP^{Sc}, the mutant *PRNP* genotype, or appropriate immunohistologic procedures and should not be excluded

in patients with atypical neurodegenerative diseases until one or preferably two of these examinations have been done.[36,39,40]

Inherited Human Prion Diseases

Genetics were first thought to have a role in Creutzfeldt-Jakob disease with the recognition that about 10% of cases are familial.[41,42] The discovery of the PrP gene and its linkage to scrapie incubation times in mice[43] raised the possibility that mutation might feature in the hereditary human prion diseases. A proline (P)→leucine (L) mutation at codon 102 was shown to be linked genetically to the development of Gerstmann-Sträussler-Scheinker disease with a lod score exceeding 3 (Figure 1).[11,12,36,44-70] This mutation may be due to the deamination of a methylated deoxycytosine (C) coupled to deoxyguanosine (G) through a phosphodiester bond (CpG) in the germline DNA encoding PrP, which results in the substitution of deoxythymine for deoxycytosine. The P102L mutation has been found in ten different families in nine different countries including the original family with Gerstmann-Sträussler-Scheinker disease.[43,71]

An insert of 144 base pairs at codon 53 containing six octarepeats was initially described in patients with Creutzfeldt-Jakob disease from four families, all residing in southern England (Figure 1).[15,40,49] The mutation is thought to have arisen through a complex series of events because the human *PRNP* gene contains only five octarepeats, indicating that a single recombination event could not have created the insert. Genealogic investigations have shown that all four families are related, arguing for a single founder born more than two centuries ago.[15] The lod score for this extended pedigree exceeds 11. Studies from several laboratories have demonstrated that two, four, five, six, seven, eight, or nine octarepeats, in addition to the normal five, are found in persons with inherited Creutzfeldt-Jakob disease,[49,50,72,73] whereas the deletion of one octarepeat has been identified without the neurologic disease.[45,46,51]

The unusually high incidence of Creutzfeldt-Jakob disease among Israeli Jews of Libyan origin was thought for many years to be due to the consumption of lightly cooked sheep brain or eyeballs.[74,75] Recent studies have shown that some Libyan and Tunisian Jews in families with Creutzfeldt-Jakob disease have a *PRNP* gene point mutation at codon 200 resulting in a glutamate (E)→lysine (K) substitution.[56,63] One patient was homozygous for the E200K mutation, but her clinical presentation was similar to that of heterozygotes,[63] arguing that familial prion diseases are true autosomal dominant disorders. The E200K mutation has also been found in Slovaks originating from Orava in north-central Slovakia,[56] in a cluster of familial cases in Chile,[76] in a large German family living in the United States,[77] and in British[78] and Japanese families.[79] Some investigators have argued that the E200K mutation originated in a Sephardic Jew whose descendants migrated from Spain and Portugal at the time of the Inquisition.[76] It is more likely that the E200K mutation has arisen independently multiple times by the deamidation of a methylated CpG as described earlier for the P102L mutation.[12,63] In support of this hypothesis are historical records of Libyan and Tunisian Jews indicating that they are descended from Jews living on the island of Jerba, where Jews first settled around 500 BC, and not from Sephardim.[80]

Many families with Creutzfeldt-Jakob disease have been found to have a point mutation at codon 178, resulting in an aspartic acid (D)→asparagine (N) substitution.[80,81] In these patients and in those with the E200K mutation, PrP amyloid plaques are rare; the neuropatho-

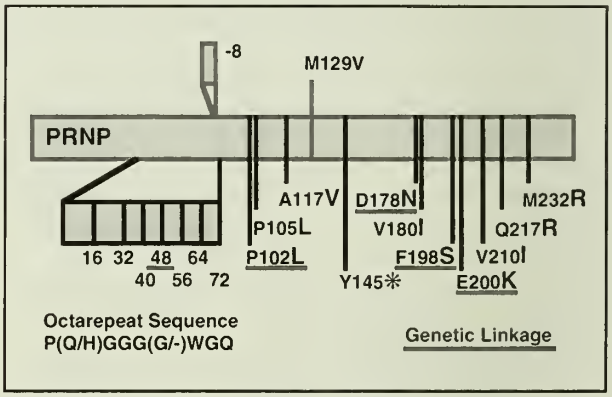

Figure 1.—Human prion protein gene (*PRNP*). The open reading frame is denoted by the large gray rectangle. Human *PRNP* wild-type polymorphisms are shown above the rectangle, and mutations that segregate with the inherited prion diseases are given below. The wild-type human prion protein gene contains five octarepeats P(Q/H)GGG(G/-)WGQ from codons 51 to 91.[44] Deletion of a single octarepeat at codon 81 or 82 is not associated with prion disease[45-47]; whether this deletion alters the phenotypic characteristics of a prion disease is unknown. There are common polymorphisms at codons 117 (alanine [Ala]→Ala) and 129 (methionine [Met]→valine [Val]); homozygosity for Met or Val at codon 129 appears to increase susceptibility to sporadic Creutzfeldt-Jakob disease.[48] Octarepeat inserts of 16, 32, 40, 48, 56, 64, and 72 amino acids at codons 67, 75, or 83 are designated by the small rectangle below the open reading frame. These inserts segregate with familial Creutzfeldt-Jakob disease, and substantial genetic linkage has been demonstrated where sufficient specimens from family members are available.[36,49-55] Point mutations are designated by the wild-type amino acid preceding the codon number and the mutant residue follows—that is, P102L. These point mutations segregate with the inherited prion diseases, and genetic linkage (underlined mutations) has been shown where sufficient specimens from family members are available. Mutations at codons 102 (proline [Pro]→leucine [Leu]), 117 (Ala→Val), 198 (phenylalanine [Phe]→serine [Ser]), and 217 (glutamine [Gln]→arginine [Arg]) are found in patients with Gerstmann-Sträussler-Scheinker disease.[12,43,55-62] Point mutations at codons 178 (aspartate [Asp]→asparagine [Asn]), 200 (glutamate [Glu]→lysine [Lys]), and 210 (Val→isoleucine [Ile]) are found in patients with familial Creutzfeldt-Jakob disease.[56,63-66] Point mutations at codons 198 (Phe→Ser) and 217 (Gln→Arg) are found in patients with Gerstmann-Sträussler-Scheinker syndrome who have prion protein amyloid plaques and neurofibrillary tangles.[11,67] Additional point mutations at codons 145 (tyrosine [Tyr]→Stop[*]), 105 (Pro→Leu), 180 (Val→Ile), and 232 (Met→Arg) have been recently reported.[68,69] The single-letter codes for amino acids are as follows: A = alanine, D = aspartate, E = glutamate, F = phenylalanine, I = isoleucine, K = lysine, L = leucine, M = methionine, N = asparagine, P = proline, Q = glutamine, R = arginine, S = serine, T = threonine, V = valine, Y = tyrosine. (Reproduced with permission from Prusiner.[70])

logic changes generally consist of widespread spongiform degeneration.

Insomnia has been described recently in multiple Italian families with the D178N mutation.[32] The neurologic disorder in these patients with fatal familial insomnia is restricted to selected nuclei of the thalamus. It is unclear whether all patients with the D178N mutation or only a subset have sleep disturbances; some of these patients have been diagnosed as having thalamic dementia.[82] Sequencing studies of DNA show that the allele with the D178N mutation encodes a methionine at position 129 in those with fatal familial insomnia, whereas a valine is encoded at position 129 in familial Creutzfeldt-Jakob disease.[83] The discovery that fatal familial insomnia is an inherited prion disease clearly widens the clinical spectrum of these disorders and raises the possibility that many other degenerative diseases of unknown cause may be caused by prions.[32]

Like the E200K and D178N(V129) mutations, a valine (V)→isoleucine (I) mutation at *PRNP* codon 210 produces Creutzfeldt-Jakob disease with classic symptoms and signs.[64,84] This V210I mutation is probably also incompletely penetrant.

Other point mutations at codons 105, 117, 145, 198, 217, and possibly 232 also segregate with inherited prion diseases.[43,57,67-69] Patients with a dementing or telencephalic form of Gerstmann-Sträussler-Scheinker disease have a mutation at codon 117. These patients and some in other families were once thought to have familial Alzheimer's disease, but are now known to have prion diseases on the basis of PrP immunostaining of amyloid plaques and *PRNP* gene mutations.[85-87] Patients with the codon 198 mutation have numerous neurofibrillary tangles that stain with antibodies to τ and have amyloid plaques[85-87] that are composed largely of a PrP fragment extending from residues 58 to 150.[88] A genetic linkage study of this family produced a lod score exceeding 6.[11] The neurologic disorder of two patients of Swedish ancestry with the codon 217 mutation[89] was similar to that of patients with the codon 198 mutation.

Patients with the Gerstmann-Sträussler-Scheinker syndrome have been reported who have a substitution of leucine for proline at PrP codon 105.[68] A patient with PrP amyloid plaques and a prolonged neurologic illness spanning almost two decades was found to have an amber mutation of the *PRNP* gene resulting in a "stop" codon at residue 145.[69] Staining of the plaques with α-PrP peptide antisera suggested that they might be composed exclusively of the truncated PrP molecules. That a PrP peptide ending at residue 145 polymerizes in amyloid filaments is to be expected, as an earlier study showed that the major PrP peptide in plaques from patients with the F198S mutation was an 11-kd PrP peptide beginning at codon 58 and ending at about 150.[88] Furthermore, synthetic PrP peptides adjacent to and including residues 109 to 122 readily polymerize into rod-shaped structures with the tinctorial properties of amyloid.[90-93]

Nomenclature for the Inherited Human Prion Diseases

Although each of the *PRNP* mutations is associated with a typical clinical presentation as noted earlier, there are a sufficient number of exceptions that a particular mutation in a single pedigree can present with symptom complexes typical of Creutzfeldt-Jakob disease in some patients and the Gerstmann-Sträussler-Scheinker syndrome in others. Because we now know the molecular basis of the disorders, it seems preferable to name them according to the mutation and to no longer refer to them as familial Creutzfeldt-Jakob disease, the Gerstmann-Sträussler-Scheinker syndrome, or fatal familial insomnia. Once the *PRNP* gene mutation has been determined, then we suggest that prion disease (P102L) be used in place of ataxic Gerstmann-Sträussler-Scheinker syndrome, such as that found in the original family with that disorder,[71,94] prion disease (E200K) instead of familial Creutzfeldt-Jakob disease in Libyan Jews, and prion disease (D178N, M129) instead of fatal familial insomnia (Table 2). These designations describe the precise causes of the disorders and remove any possible ambiguities.

The need to designate the inherited prion diseases by their mutations (molecular lesions) is emphasized by the vastly different clinical presentations and postmortem neurologic disorders noted in four afflicted members of a family with prion disease (6 octarepeat insert).[40] One of the four family members with the insert had a classic case of Creutzfeldt-Jakob disease and had pronounced spongiform change in the cerebral cortex, whereas another

TABLE 2.—*Inherited Prion Diseases of Humans*

Proposed Designation	*Alternative Name*
Inherited prion disease (P102L)	Gerstmann-Sträussler-Scheinker disease
Inherited prion disease (P105L)	Gerstmann-Sträussler-Scheinker disease
Inherited prion disease (A117V)	Gerstmann-Sträussler-Scheinker disease
Inherited prion disease (Y145Stop)	Gerstmann-Sträussler-Scheinker disease
Inherited prion disease (D178N)	Familial Creutzfeldt-Jakob disease, familial fatal insomnia
Inherited prion disease (V180I)	Gerstmann-Sträussler-Scheinker disease
Inherited prion disease (F198S)	Gerstmann-Sträussler-Scheinker disease
Inherited prion disease (E200K)	Familial Creutzfeldt-Jakob disease
Inherited prion disease (V210I)	Familial Creutzfeldt-Jakob disease
Inherited prion disease (Q217R)	Gerstmann-Sträussler-Scheinker disease
Inherited prion disease (octarepeat insert)	Familial Creutzfeldt-Jakob disease

presented with ataxia and had numerous PrP amyloid plaques at autopsy. The second case might have been called Gerstmann-Sträussler-Scheinker disease with hesitation. The third and fourth members of the family died in hospitals with the diagnosis of dementia, but had no spongiform change at autopsy and were not given the diagnosis of Creutzfeldt-Jakob disease.

Human *PRNP* Gene Polymorphisms

At *PRNP* codon 129, a polymorphism encodes either methionine (M) or valine (V) (Figure 1).[95] This polymorphism appears able to influence prion disease expression not only in inherited forms, but also in iatrogenic and sporadic forms of prion disease.

Susceptibility to infection may be partially determined by the *PRNP* codon 129 genotype,[96] analogous in principle to the incubation-time alleles in mice.[96,97] Population frequencies for the codon 129 polymorphism in whites are 12% V/V, 37% M/M, and 51% M/V.[48] In 16 patients (15 white, 1 black) from the United Kingdom, the United States, and France with iatrogenic Creutzfeldt-Jakob disease from contaminated growth hormone extracts, eight (50%) were V/V, five (31%) were M/M, and three (19%) were M/V.[96] Thus, a disproportionate number of patients with iatrogenic Creutzfeldt-Jakob disease were homozygous for valine at *PRNP* codon 129. Heterozygosity at codon 129 may provide partial protection. Whether these associations are strongly significant awaits statistical analysis of larger samples. Thousands of children who received pituitary growth hormone extracts are still at risk for the development of Creutzfeldt-Jakob disease. Fortunately, the use of genetically engineered growth hormone will eliminate this iatrogenic form of the disease.

No specific mutations have been identified in the *PRNP* gene of patients with sporadic Creutzfeldt-Jakob disease. Patients with the sporadic form, however, are largely homozygous at codon 129.[48] This finding supports a model of prion production that favors PrP interactions between homologous proteins, as appears to occur in transgenic mice expressing Syrian hamster PrP inoculated with either hamster prions or mouse prions,[10,98,99] as well as

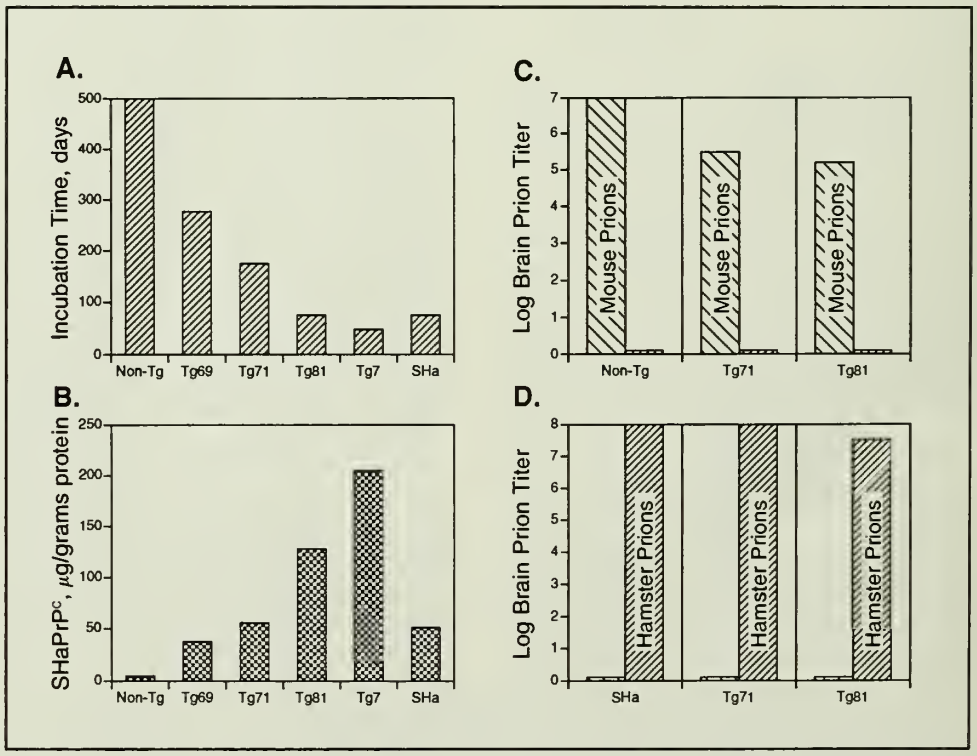

Figure 2.—Transgenic (Tg) mice expressing Syrian hamster (SHa) prion protein (PrP) exhibit species-specific scrapie incubation times, infectious prion synthesis, and neurologic abnormalities.[99] **A**, Scrapie incubation times are shown in nontransgenic mice (Non-Tg) and 4 lines of Tg mice expressing SHaPrP and Syrian hamsters inoculated intracerebrally with about 10^7 of a median infectious dose of Sc237 prions serially passaged in Syrian hamsters. The 4 lines of Tg mice have different numbers of transgene copies: Tg69 and Tg71 mice have 2 to 4 copies of the SHaPrP transgene, whereas Tg81 have 30 to 50 and Tg7 mice have more than 60. Incubation times are the number of days from inoculation to the onset of neurologic dysfunction. **B**, Brain Syrian hamster cellular prion protein ($SHaPrP^C$) levels are shown in Tg mice and Syrian hamsters. The $SHaPrP^C$ levels were quantitated by an enzyme-linked immunoassay. **C**, Prion titers were measured in brains of clinically ill animals after inoculation with mouse prions. Brain extracts from Non-Tg, Tg71, and Tg81 mice were bioassayed for prions in mice (left) and hamsters (right). **D**, Prion titers were measured in brains of clinically ill animals after inoculation with SHa prions. Brain extracts from Syrian hamsters as well as Tg71 and Tg81 mice were bioassayed for prions in mice (left) and hamsters (right). (Reproduced with permission from Prusiner.[110])

transgenic mice expressing a chimeric mouse/hamster PrP transgene inoculated with "artificial" prions.[100]

Ataxia develops as an early sign in about 15% of patients with sporadic Creutzfeldt-Jakob disease, accompanied by dementia.[101] Most but not all patients with ataxia have compact (kuru) plaques in the cerebellum.[102] Patients with ataxia and compact plaques have a protracted clinical course that may last as long as three years. The molecular basis for the differences between Creutzfeldt-Jakob disease of shorter and longer duration has not been fully elucidated, but some preliminary analyses have suggested that patients with protracted, atypical clinical courses are more likely to be heterozygous at codon 129.[103,104]

Homozygosity at codon 129 has been reported to be associated with an earlier age of onset in patients with the inherited prion disease caused by the 6 octarepeat insert, but not that caused by the E200K mutation in Libyan Jews.[14,105] As noted earlier, the phenotype for fatal familial insomnia is found in patients with the D178N mutation who encode a methionine at codon 129 on the mutant allele, whereas those with dementing illness (familial Creutzfeldt-Jakob disease) encode a valine at 129.[83] Homozygosity for either M or V at codon 129 is thought to be associated with an earlier age of onset for the D178N mutation.

Barriers for the Transmission of Prion Diseases

The passage of prions between species is a stochastic process characterized by prolonged incubation times.[106] Prions synthesized de novo reflect the sequence of the host PrP gene and not that of the PrP^{Sc} molecules in the inoculum.[107] On subsequent passage in a homologous host, the incubation time shortens to that recorded for all subsequent passages, and it becomes a nonstochastic process. The species-barrier concept is of practical importance in assessing the risk for Creutzfeldt-Jakob disease developing in humans after the consumption of scrapie-infected lamb or from cattle with bovine spongiform encephalopathy.[108,109]

To test the hypothesis that differences in PrP gene sequences might be responsible for the species barrier, transgenic mice expressing Syrian hamster (SHa) PrP were constructed.[98,99] The PrP genes of Syrian hamsters and mice encode proteins differing at 16 positions. Incubation times in four lines of transgenic SHaPrP mice inoculated with mouse prions were prolonged compared with those observed for nontransgenic control mice. Inoculation of transgenic SHaPrP mice with SHa prions showed abrogation of the species barrier, resulting in abbreviated incubation times due to a nonstochastic process (Figure 2-A).[98,99,110] The length of the incubation time after inoculation with SHa prions was inversely proportional to the level of $SHaPrP^{c}$ in the brains of transgenic SHaPrP mice (Figure 2-B).[99] The levels of $SHaPrP^{Sc}$ in the brains of clinically ill mice were similar in all four transgenic SHaPrP lines inoculated with SHa prions. Bioassays of brain extracts from clinically ill transgenic SHaPrP mice inoculated with mouse prions revealed that only mouse prions but no SHa prions were produced (Figure 2-C). Conversely, inoculation of transgenic SHaPrP mice with SHa prions led to only the synthesis of SHa prions (Figure 2-D). These findings contend that the amino acid sequence of PrP^{Sc} in the inoculum specifies whether mouse PrP or $SHaPrP^{C}$ will be converted into PrP^{Sc} in recipient transgenic SHaPrP mice. Furthermore, the production of PrP^{Sc} appears to involve the formation of an intermediate complex between homotypic PrP^{C} and PrP^{Sc}.

The neurologic abnormalities of transgenic SHaPrP mice were also found to be determined by the genetic origin of prion inoculum. Mouse prions injected into transgenic SHaPrP mice produced a neurologic abnormality characteristic of mice with scrapie. A moderate degree of vacuolation in both the gray and white matter was found, but amyloid plaques were rarely detected. Inoculation of transgenic SHaPrP mice with SHa prions produced intense vacuolation of the gray matter, sparing of the white matter, and numerous SHaPrP amyloid plaques characteristic of Syrian hamsters with scrapie.

Transgenic Mice Overexpressing Wild-type PrP Genes

During transgenetic studies, we discovered that uninoculated older mice harboring high copy numbers of wild-type PrP transgenes derived from Syrian hamsters, sheep, and PrP-B mice spontaneously developed truncal ataxia, hind-limb paralysis, and tremors.[111] These transgenic mice showed a profound necrotizing myopathy involving skeletal muscle, a demyelinating polyneuropathy, and focal vacuolation of the central nervous system. The development of disease was dependent on transgene dosage. For example, transgenic $(SHaPrP^{+/+})7$ mice homozygous for the SHaPrP transgene array regularly developed disease between 400 and 600 days of age whereas hemizygous transgenic $(SHaPrP^{+/0})7$ mice developed disease only after more than 650 days.

Attempts to demonstrate PrP^{Sc} in either muscle or brain were unsuccessful, but the transmission of disease with brain extracts from transgenic $(SHaPrP^{+/+})7$ mice inoculated into Syrian hamsters did occur. These Syrian hamsters had PrP^{Sc} as detected by immunoblotting and spongiform degeneration (D. Groth and S. B. Prusiner, unpublished data, June 1993). Serial passage with brain extracts from these animals to recipients was observed. De novo synthesis of prions in transgenic $(SHaPrP^{+/+})7$ mice overexpressing wild-type $SHaPr^{Pc}$ provide support for the hypothesis that sporadic Creutzfeldt-Jakob disease does not result from infection, but rather is a consequence of the spontaneous, although rare, conversion of PrP^{C} into PrP^{Sc}. Alternatively, a somatic mutation in which mutant $SHaPrP^{C}$ is spontaneously converted into PrP^{Sc}, as in the inherited prion diseases, could also explain sporadic Creutzfeldt-Jakob disease. These findings as well as those described earlier for transgenic mice with mouse PrP(P101L) strongly suggest that prions are devoid of foreign nucleic acid, in accord with many earlier studies that use other experimental approaches.[10]

Conclusions and Prospects for Therapy

Knowledge accrued from the study of prion diseases may provide an effective strategy for defining the causes and dissecting the molecular pathogenesis of the more common neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Advances in the molecular genetics of Alzheimer's disease and amyotrophic lateral sclerosis suggest that, like the prion diseases, an important subset is caused by mutations that result in nonconservative amino acid substitutions in proteins expressed in the central nervous system.

At present, there are no effective therapies for the treatment of prion diseases. These disorders are invariably fatal. The inherited prion diseases can be prevented by genetic counseling coupled with prenatal DNA screening, but such testing may present ethical problems. For example, during the childbearing years, prospective parents are generally symptom free and may not want to know their own gene types. The apparent incomplete penetrance of some of the inherited prion diseases makes predicting the future for an asymptomatic person uncertain.[14,63,76]

Ablation of the PrP gene in transgenic Prn-$p^{0/0}$ mice has not affected the development of these animals, and they remain healthy at 2 years of age.[112] Because the absence of PrP^{C} expression does not provoke disease, we can conclude that scrapie and other prion diseases are a consequence of PrP^{Sc} accumulation rather than an inhibition of PrP^{C} function. To date, the function of PrP^{C} remains unknown.

The resistance of Prn-$p^{0/0}$ mice to prions and their failure to propagate scrapie infectivity have prompted suggestions that gene therapy or antisense oligonucleotides might ultimately provide an effective therapeutic approach.[113,114] Mice heterozygous (Prn-$p^{0/+}$) for ablation of the PrP gene have prolonged incubation times when inoculated with mouse prions. This finding is in accord with studies of transgenic SHaPrP mice where decreased SHaPrP expression was accompanied by prolonged incubation times.[99]

Because the delivery of therapeutic polynucleotides to the central nervous system remains problematic, the most effective therapy may evolve from the development of drugs that block the conversion of PrP^{C} into PrP^{Sc}. Because the fundamental event in both the formation of PrP^{Sc} and the propagation of prions seems to be the unfolding of α-helices and their refolding into β-sheets,[20] drugs targeting this structural transformation would seem likely to be efficacious.

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NEUROLOGY Discovery

Mapping Human Brain Activity In Vivo

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A wide range of structural and functional techniques now exists to map the human brain in health and disease. These approaches span the gamut from external tomographic imaging devices (positron-emission tomography, single photon-emission computed tomography, magnetic resonance imaging, computed tomography), to surface detectors (electroencephalography, magnetoencephalography, transcranial magnetic stimulation), to measurements made directly on the brain's surface or beneath it (intrinsic signal imaging, electrocorticography). The noninvasive methods have been combined to provide unique and previously unavailable insights into the macroscopic organization of the functional neuroanatomy of human vision, sensation, hearing, movement, language, learning, and memory. All methods have been applied to patients with neurologic, neurosurgical, and psychiatric disease and have provided a rapidly expanding knowledge of the pathophysiology of diseases such as epilepsy, cerebrovascular disease, neoplasms, neurodegenerative diseases, mental illness, and addiction states. In addition, these new methods have become a mainstay of preoperative surgical planning and the monitoring of pharmacologic or surgical (transplantation) interventions. Most recently, the ability to observe the reorganization of the human nervous system after acute injury, such as occurs with cerebral infarction or head trauma, or in the course of a progressive degenerative process such as Alzheimer's or Parkinson's disease, may provide new insights and methods in the rapidly expanding field of neurorehabilitation. Our newfound ability to generate maps and databases of human brain development, maturation, skill acquisition, aging, and disease states is both an exciting and formidable task.

(Mazziotta JC: Mapping human brain activity in vivo, *In* Neurology—From Basics to Bedside [Special Issue]. West J Med 1994; 161:273-278)

Brain mapping in its broadest sense encompasses all data relevant to the understanding of the structure and function of the nervous system. Recent advances in a wide range of technologies have made the concept of mapping the human brain, at least at the macroscopic level, a reality. These rapidly developing methods, combined with the "Decade of the Brain" and "Human Brain Project" initiatives, should result in cooperation and collaboration among groups. The development and application of these new techniques will lead to an integrated approach to collecting, storing, and exchanging data relevant to the study of normal brain function and diseases that perturb it.[1]

Methods relevant to human brain mapping can be divided into two major categories: structural and functional (Table 1). All of these techniques have been applied to the study of the human brain. When assessing brain mapping methods, it is useful to keep in mind the following variables: spatial and temporal resolution, sampling—the volume of tissue surveyed for a given measurement—whether the technique is applied postmortem or in vivo, the requirement for anesthesia, repeatability, and, if repeatable, the minimal interval between studies. A brief description of some of the methods more commonly employed for mapping the human brain follows. For more complete descriptions of a number of these methods, several reviews have been recently published.[2-9]

Brain Mapping Technologies

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) was introduced into research and medical practice in the early 1980s. The excellent spatial resolution, including high contrast between gray and white matter, and the ability to sample the intracranial contents at any planar angle represented great steps forward in human structural brain imaging. By adjusting radio-frequency pulse sequences, a wide range of anatomical images can be produced that reflect proton distributions, overwhelmingly predominated by water molecules, in health and in disease.[6]

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ABBREVIATIONS USED IN TEXT

EEG = electroencephalography
MEG = magnetoencephalography
MRI = magnetic resonance imaging
MRS = magnetic resonance spectroscopy
PET = positron-emission tomography
SPECT = single photon-emission computed tomography

Magnetic resonance angiography. The development of MRI pulse sequences that exaggerated the diminished signal from vascular compartments containing flowing blood resulted in images that demonstrated these vascular spaces.[7,8,10] The result is a three-dimensional, digitally sampled image of the medium- and large-diameter arteries and veins. Because magnetic resonance angiographic

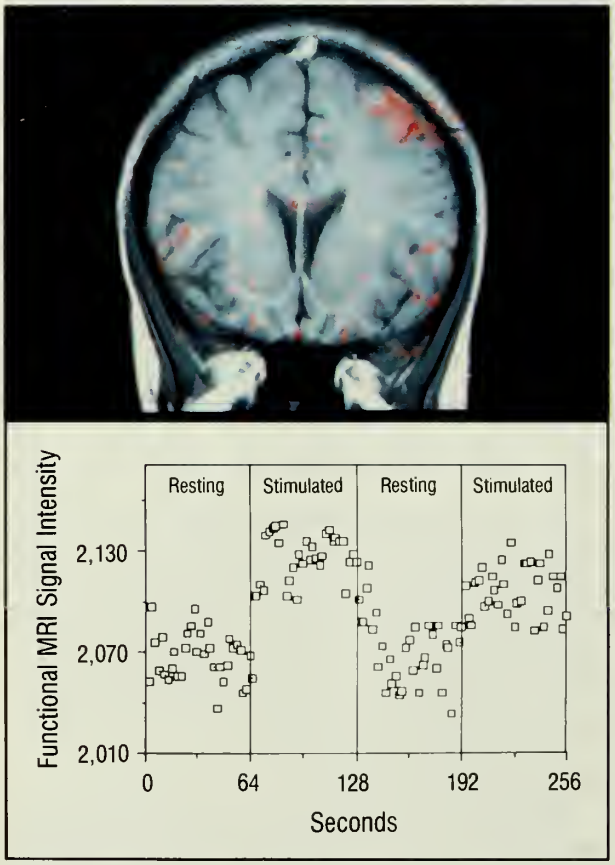

Figure 1.—A functional magnetic resonance image (MRI) was taken of a normal subject performing a motor task. **Top,** The coronal image of a normal subject is taken through the motor cortex during the performance of a motor task with the right hand. The left hemisphere is on the reader's right. Note the increased signal in the primary motor cortex in the hand area of the left hemisphere, shown in red. **Bottom,** The functional MRI signal intensity in the left hemisphere motor area when the subject alternately rested and moved the right hand is plotted. These measurements of the motor response time course were obtained without administering ionizing radiation or exogenous contrast material but merely by measuring differences in oxygenation of hemoglobin concentrations of the venous blood in the brain tissue. See text for details. (Photographs courtesy of C. Stern, PhD; K. Kwong, PhD; Bruce Rosen, PhD; J. Belliveau, PhD; Mark Cohen, PhD, MGH-NMR Center, Charlestown, Massachusetts.)

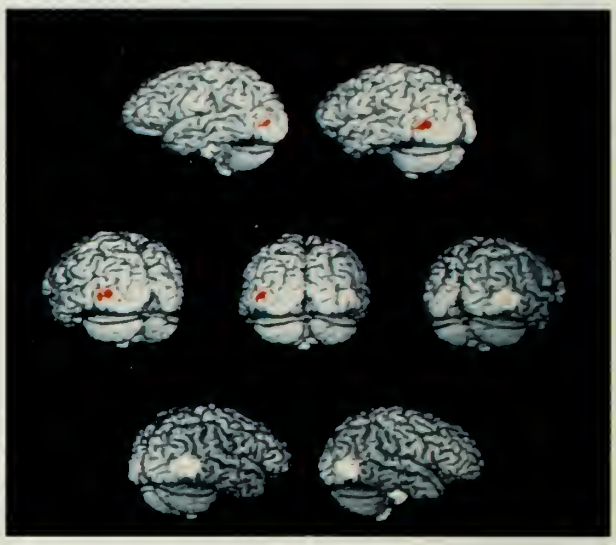

Figure 2.—Brain mapping is used in the study of normal vision. Seven views are shown of the 3-dimensionally rendered brain of a single normal subject performing a visual task. The structural anatomy image is derived from serial magnetic resonance imaging studies that have been 3-dimensionally rendered with the skull and meninges removed. The red areas indicate substantial increases in cerebral blood flow derived from positron-emission tomography when this subject observed a moving visual stimulus as compared with a stationary visual stimulus. The result demonstrates 2 regions at the junction of the temporal and occipital lobes critical to processing and interpreting visual motion. Damage to these areas leads to a behavioral syndrome where patients misunderstand visual information that is moving. Experiments in monkeys have demonstrated a visual motion center in a homologous portion of the brain (from Watson et al[22]).

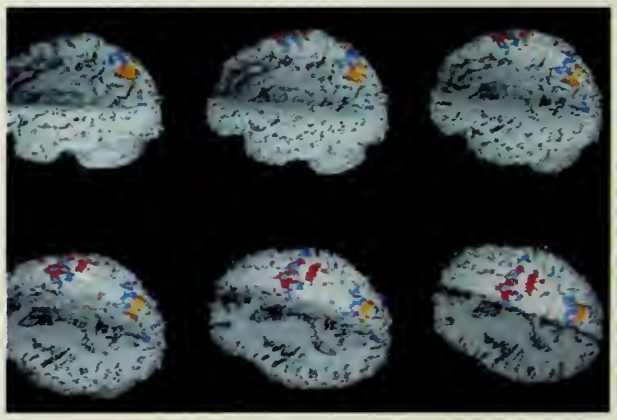

Figure 3.—Six views are taken of a patient with an arteriovenous malformation shown in orange in the right parietal lobe. Structural brain anatomy was derived from serial magnetic resonance imaging studies and rendered after removal of the skull, scalp, and meninges. The left hemisphere has been digitally removed. As part of this patient's preoperative surgical planning, positron-emission tomographic measurements of substantial increases in cerebral blood flow were made while he performed visual motor tasks. The blue area depicts the blood flow responses that occurred when the patient followed a moving target on a computer monitor with his eyes only. The magenta color demonstrates the additional sites that were active when he followed the target with both his eyes and the index finger of his left hand. By avoiding critically functioning areas during surgical resections, it is possible to minimize postoperative deficits in patients with lesions in or close to key cortical regions (from Grafton et al[33]).

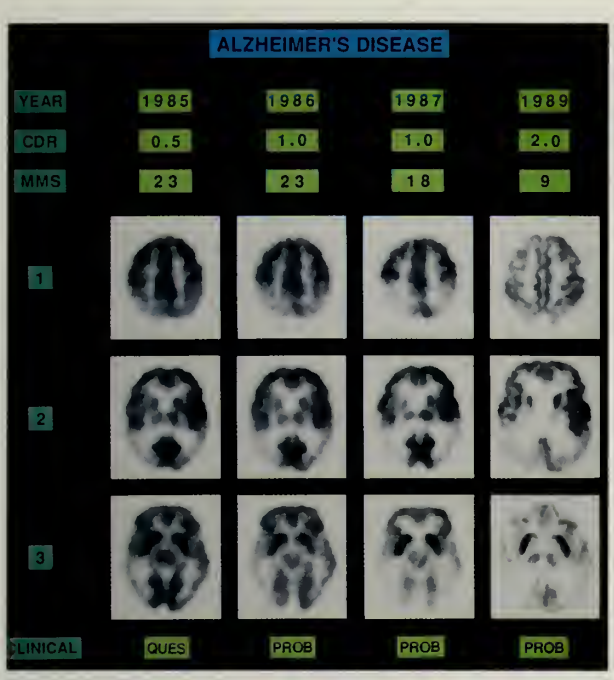

Figure 4.—Brain mapping is done for neurodegenerative diseases of the brain. Serial positron-emission tomographic images show glucose metabolism in a single patient in 1985, 1986, 1987, and 1989. The patient ultimately died, and autopsy confirmed the presence of Alzheimer's disease. Each row shows a different anatomical level, and each column represents a different point in time. The blacker the image, the higher the metabolic rate for glucose. In the earliest study, when the patient had only memory deficits and no other confirmatory features of Alzheimer's disease, a defect in glucose metabolism in the parietal lobe and superior temporal cortices was already present. With disease progression, the spatial extent and magnitude of this hypometabolism progresses to the point where, in 1989 just before he died, the patient had profound and widespread neocortical hypometabolism. These changes match the clinical deterioration of the patient over time.

Such maps provide a picture of the changes caused by the disorder over time. Knowledge of this rate of change sequence allows for research in the natural history of degenerative diseases and serves as a prelude for determining the effectiveness of experimental therapies and behavioral as well as pharmacologic interventions aimed at slowing or compensating for such disease processes (from Mazziotta et al[34]). CDR = Clinical Dementia Rating Scale, MMS = Mini-Mental Scale

data are three dimensional and digital, they can be combined with MRI data sets to produce composite images of both parenchymal and vascular neuroanatomy in a single synthetic image. These methods have been used to characterize and identify occlusive cerebrovascular disease of the carotid arteries in the cervical region as well as the presence of arteriovenous malformations and aneurysms that occur intracranially.

Magnetic resonance spectroscopy. It has now been clearly demonstrated that magnetic resonance spectroscopic (MRS) studies of the brain can be done using conventional clinical imaging instruments.[6,11-15] Although proton spectra have been most widely applied, other isotopes that generate nuclear magnetic resonance spectra include carbon 13, sodium 23, fluorine 19, and phosphorus 31. Human brain studies with MRS have included the

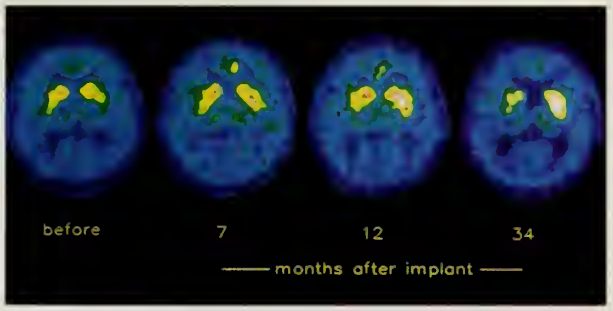

Figure 5.—The images illustrate the neurochemistry of Parkinson's disease and the monitoring of experimental therapy. Serial images were obtained from positron-emission tomography (PET) and ^{18}F-labeled levodopa in a patient with Parkinson's disease studied preoperatively and then at 7, 12, and 34 months following the implantation of fetal substantia nigra tissue into the right putamen. Note that in the preoperative PET image (**before**), there is a relative reduction in the uptake of ^{18}F-labeled levodopa in the right putamen. Note further that there is a serial increase in this uptake at each interval following the surgical implantation of the nigral tissue. Concomitantly, there is a progressive deterioration of the contralateral and untreated putamen. These changes paralleled clinical improvement of the patient following transplantation. Such studies demonstrate the ability of brain mapping methods not only to confirm clinical diagnoses and select patients for therapy, but also to monitor experimental and conventional therapies to understand their mechanism of action and correlate these changes with clinical improvements in patients.[35,36] (Photo courtesy of Richard Frackowiak, MD, and Guy Sawle, MD, Hammersmith Hospital, MRC Cyclotron Unit, London, United Kingdom.)

observation of increments in lactate concentrations during brain activation by behavioral tasks.[16] In addition, MRS has been used to assess neurodegenerative diseases, epilepsy, and cerebral neoplasms. Such studies allow for the detection of signals from brain metabolites present at millimolar concentrations.

Functional MRI. Within the past five years, MRI has been used to make functional maps of changes in cerebral venous oxygen concentrations that correlate with neuronal activity. Such approaches require fast two-dimensional brain imaging.[17-19] Using echo-planar imaging, two-dimensional slice data can be obtained in 40 millisec-

TABLE 1.—*Brain Mapping Methods Used in Humans*

Category	*Imaging Method*
Structural	X-ray computed tomography
	Magnetic resonance imaging
	Magnetic resonance angiography
Functional	
Noninvasive	Positron-emission tomography
	Single photon-emission computed tomography
	Functional magnetic resonance imaging
	Magnetic resonance spectroscopy
	Electroencephalography
	Magnetoencephalography
	Transcranial magnetic stimulation
Invasive	Electrocorticography
	Depth electrodes
	Cortical stimulation
	Optical signal imaging

onds with an in-plane anatomical resolution of about 1 mm. This technique was originally used with exogenous contrast enhancement from gadolinium,[20] but has been extended to measuring intrinsic signals that occur as a result of differential concentrations of deoxyhemoglobin in venous blood in brain regions that increase their neuronal activity.[21] Thus, functional maps of the human brain can be obtained without ionizing radiation or the requirement to administer exogenous contrast material. These techniques have already been used to evaluate patients with epilepsy and normal subjects performing visual, motor, sensory, and language tasks (Figure 1).

Positron-Emission Tomography

Developed in the mid-1970s, research applications for positron-emission tomography (PET) originally focused on the functional neuroanatomy of the brain.[3,9] Clinical use did not begin in earnest until the late 1980s. With PET, positron-emitting isotopes are typically produced at a local cyclotron because their half-lives are so short, ranging from seconds to minutes. These isotopes are then chemically integrated into radiopharmaceuticals with known biologic behavior. The resultant compounds are administered intravenously or inhaled by subjects, and data are collected by the PET instrument as two-dimensional tomographic maps. Typical isotopes include oxygen 15, carbon 11, nitrogen 13, and fluorine 18. This technique is, by its very nature, biochemical and physiologic. The only limit to the number of different processes that can be examined with PET is the ingenuity of chemists to develop new compounds and for physiologists to validate them. Currently PET is used to measure cerebral metabolism, blood flow and volume, oxygen use, neurotransmitter synthesis, and receptor binding. Its spatial resolution is approximately $5 \times 5 \times 5$ mm. Modern tomographs are able to sample the entire intracranial contents, and studies can be repeated as frequently as every ten minutes with the ultrashort half-lived isotopes (^{15}O), and with the proviso that ionizing radiation is being administered at each session. Studies of cerebral activation using PET have provided new insights into the functional neuroanatomy of sensory, motor, language, and memory processes (Figure 2). Further, PET has elucidated the metabolic, hemodynamic, and biochemical events that occur with epilepsy; cerebrovascular disease; degenerative disorders such as Alzheimer's, Parkinson's, and Huntington's diseases; and psychiatric disorders such as affective diseases, obsessive-compulsive disorder, and schizophrenia.[3]

Single Photon-Emission Computed Tomography

Single photon-emission computed tomography (SPECT) instruments were developed in the 1950s and 1960s and were immediately applied to studies of cerebral function.[23] Like PET, SPECT uses radiopharmaceutical agents administered intravenously or by inhalation to evaluate function in the human brain. These radiopharmaceuticals incorporate isotopes that emit single-photon radiation, most particularly in the form of gamma rays. Radioisotopes used with SPECT include xenon 133, iodine 123, technetium 99m, and others. The longer half-lives of these isotopes do not require their on-site production. Most modern hospitals have SPECT instruments available, and radiopharmaceuticals are purchased from regional distribution centers. Though less quantifiable than PET, SPECT provides estimates of cerebral perfusion, blood volume, and receptor distribution. The SPECT techniques currently have a spatial resolution of about $9 \times 9 \times 9$ mm. Using appropriate scanning protocols, the entire intracranial contents can be sampled with these devices. Like PET, SPECT imaging has been applied to normal brain function, epilepsy, cerebrovascular disease, degenerative disease processes, and psychiatric syndromes.

Electroencephalography

Developed and perfected for clinical use in the early part of the 20th century, electroencephalography (EEG) has been a mainstay in certain neurologic diagnoses. Signal averaging with the EEG and statistical approaches to assess the component parts of the EEG signal have resulted in its use in a wide variety of cortical mapping approaches. Largely limited to surface dipoles, the approach generally reflects neuronal activity in the superficial layers of the cerebral cortex, and the signal is distorted by volume conductance within tissue and through the skull. Spatial resolution with the technique is determined by the density of electrode placements, but typically is on the order of a few square centimeters at the cortical surface. Temporal resolution is exquisite and comparable to the time frames of neuronal events (milliseconds). Electroencephalographic data can be combined with MRI and functional imaging data sets to take advantage of the excellent temporal resolution of the former. The application of electrodes directly on the surface or into the depth of brain tissue—electrocorticography—increases the spatial resolution because it eliminates the distorting features of electrical conductance through the skull. Temporal resolution remains unchanged, but sampling is limited to the exposed surface of the cortex. With depth electrodes the spatial resolution can be increased to a volume as small as 100 μm^3, with an attendant reduction in sampling. The invasive nature of these last two techniques limits their use to patients who are undergoing surgical procedures.

Magnetoencephalography

Magnetoencephalography (MEG) takes advantage of the fact that the weak electrical fields in the brain that are detected by EEG also induce a magnetic field that can be externally measured. The extremely low magnitude of these fields requires the use of supercooled devices in rooms that are isolated from the external magnetic and electrical environment. Because magnetic rather than electrical fields are detected using MEG, distortion caused by the effects of the skull is eliminated. Proponents stress that this lack of distortion allows for more accurate localization of electrical activity three-dimensionally in the brain. A comparison of EEG and MEG

techniques in human patients with implanted current sources—such as patients with epilepsy with implanted electrodes before an operation—showed a comparable spatial localization accuracy for the two methods.[24] As with EEG, MEG has a temporal resolution in the millisecond time frame.

Optical Signal Imaging

A variety of techniques can be grouped under the heading "Optical Signal Imaging." These include techniques that measure changes in voltage-dependent dyes, fluorescent ion concentration, energy absorbents dependent on the reduced form of nicotinamide-adenine dinucleotide, and visible or infrared light reflected or emitted from the surface that can be related to blood flow.[25-30] The last method has been developed in animal models over the past decade. These approaches have recently been used for intraoperative measurements of functional activity, but the available data are limited, and no general conclusions can yet be provided. The obvious disadvantage of these approaches is that they require exposure of the cortical surface, thus limiting their use to intraoperative examinations of patients who require surgical therapy and, as such, are not normal subjects.

Integrating Methods

As can be seen from the preceding section, each brain mapping method has its own advantages and disadvantages. The combination of multimodality data sets allows the attributes of each technique to be exploited while, in composite, limiting their disadvantages. Data can be integrated for a given patient across modalities or by grouping patients into a common average.[31,32]

For example, within-subject integration in a patient with a brain tumor or an arteriovenous malformation can be useful in presurgical planning in avoiding injury or the resection of normally functioning and critical brain structures (Figure 3).[33] A distribution map of the neuroanatomy of the patient's brain can be obtained from MRI, vascular anatomy superimposed from magnetic resonance angiography, and functionally important sites for sensory, motor, or language tasks derived from PET, SPECT, or functional MRI. In the case of brain tumors, chemical information can be derived from PET or MRS. A three-dimensional composite map of these data sets can be synthesized for a patient and displayed in the operating room as a guide to surgical resection. Further, intraoperative measurements using EEG or intrinsic signal mapping can confirm the preoperative maps at the time of the operation.

By averaging among subjects, common sites of activations in the normal brain can be determined and their individual variation defined. Such approaches will lead to a better understanding of the general organization of brain function and how those maps change with development, aging, disease processes, or recovery after injury. In patients, serial images in the process of disease progression or during recovery following an acute injury such as from cerebral infarction or head trauma can demonstrate the temporal sequence of events that occur as the three-dimensional functional systems in the brain become reorganized.

By providing serial images, functional imaging studies have led to new insights into the spatial and temporal processes that occur during disease progression. Such maps have been demonstrated in Alzheimer's disease (Figure 4),[34] Huntington's disease, and Parkinson's disease. In Parkinson's disease, PET studies using an ^{18}F-labeled analogue of levodopa have shown that the loss of dopamine-synthesizing capacity begins in the posterior putamen and spreads anteriorly toward the caudate. Useful in confirming an early diagnosis or in the differential diagnosis of overlapping parkinsonian syndromes, these brain mapping studies have also provided an important means of monitoring experimental therapy using fetal substantia nigral transplants into patients with Parkinson's disease (Figure 5).[35,36]

The recovery of function of the human nervous system after injury has been carefully studied from a clinical and a behavioral perspective. Brain mapping techniques now provide a means to examine the abnormalities of this functional reorganization in a much more detailed fashion. For example, Chollet and colleagues examined patients who had small subcortical cerebral infarctions that resulted in weakness of an upper extremity.[37] After their clinical recovery, when strength had returned to the arm, PET measurements of cerebral blood flow were made when patients performed a motor task with their recovered arm, and these measurements were compared with those made when the patient performed the identical task with the normal, contralateral arm. With the normal arm, blood flow increased in primary and premotor cortices contralateral to the moving arm and in the ipsilateral cerebellum. When the recovered arm did the task, however, the responses in the contralateral primary and premotor cortices were reduced from the expected level. In addition, ipsilateral primary and premotor cortices and bilateral sites in the cerebellum were active. This represented an important first demonstration that with the recovery of function in the nervous system, not only can the original pathway subserve function but also homologous parallel pathways on the opposite side of the brain appear to participate in the recovery process. These types of observations should lead to more pathophysiologically based approaches to the behavioral and pharmacologic treatment of patients with brain injuries.

Conclusions and Future Prospects

Many of the methods described in this brief article have been developed only in the past 10 to 15 years, and a number have come into clinical use only in the past 18 months. Much effort and innovation have been applied during that time to refining the techniques themselves. Effort has now shifted so that the application of these techniques to important basic science and clinical questions is now the mainstay of activities in brain mapping laboratories worldwide. It is anticipated that these techniques will rapidly yield a vastly improved macroscopic map of the systemwide distributions of functional neuroanatomy in the normal brain

during development, adult life, and aging. The functional organization of human sensory, motor, language, and cognitive systems will be revealed for the first time.

Clinical evaluations of patients will, with greater regularity, have a functional imaging component. These clinical studies will improve the physiologic and biochemical diagnostic accuracy and early disease detection. They will be used to monitor not only experimental and conventional therapies but also the natural reorganization of function in injured human brains.

It is predicted that conventional MRI devices will be refitted to take advantage of functional and spectroscopic techniques. The PET and SPECT instruments will be used to evaluate epilepsy in patients who are surgical candidates, characterize brain tumors, and provide the differential diagnosis for degenerative brain disorders. The combined use of functional tomographic methods with EEG, MEG, and optical intrinsic signal imaging will provide spatial resolution measurements on the order of a few millimeters, with temporal resolution in the millisecond range.

These new areas of research and clinical application will provide exciting new insights into normal brain function, the diseases that disrupt it, and the range of therapeutic interventions that seek to restore normal function in patients with neurologic, neurosurgical, and psychiatric disorders.

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Neurologic Effects of Alcoholism

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Alcoholism, a worldwide disorder, is the cause of a variety of neurologic disorders. In this article we discuss the cellular pathophysiology of ethanol addiction and abuse as well as evidence supporting and refuting the role of inheritance in alcoholism. A genetic marker for alcoholism has not been identified, but neurophysiologic studies may be promising. Some neurologic disorders related to long-term alcoholism are due predominantly to inadequate nutrition (the thiamine deficiency that causes Wernicke's encephalopathy), but others appear to involve the neurotoxicity of ethanol on brain (alcohol withdrawal syndrome and dementia) and peripheral nerves (alcoholic neuropathy and myopathy).

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Alcoholism is characterized by addiction to alcohol. Persons with this addiction crave alcoholic beverages and develop tolerance to its intoxicating effects. When they stop drinking, neurologic signs of withdrawal develop. This withdrawal syndrome is evidence of a physical dependence on ethanol. Alcohol abuse refers to recurrent episodes of excessive drinking despite serious economic, social, or medical consequences. Alcohol abuse does not usually produce physical dependence.[1]

Alcoholism is a worldwide disorder of enormous cost to society. In the United States more than 20% of hospital admissions involve medical complications of excessive drinking, and the annual socioeconomic cost of alcoholism is about $100 billion.[1] Persons with alcoholism have serious medical complications and commonly have alcoholic neurologic disorders. Most of these disorders, except Wernicke's disease, appear to be due to the neurotoxicity of ethanol.[2] Wernicke's encephalopathy is caused by thiamine deficiency, but genetic factors may play a role in affected patients. We review current concepts about the pathogenesis of alcoholism, alcoholic neurologic disorders, and genetic factors that may predispose persons to alcoholism and brain damage.

Pharmacology

Ethanol enters the circulation within minutes of drinking and is quickly distributed throughout the body.[3] Virtually all alcohol is metabolized in the liver, where alcohol dehydrogenase converts ethanol to acetaldehyde, which, in turn, is metabolized by aldehyde dehydrogenase to acetate. An excessive accumulation of acetaldehyde causes an "alcohol-flush" reaction. This occurs in about 50% of Japanese and other Asians because they have a less active aldehyde dehydrogenase isoenzyme.[4] Affected persons experience hot sensations associated with vasodilatation and facial flushing, tachycardia, and hypotension. Possibly because of these unpleasant experiences, Japanese people with reduced aldehyde dehydrogenase activity have a lower rate of alcoholism.[4]

Disulfiram (Antabuse) inhibits aldehyde dehydrogenase and has been used prophylactically to discourage drinking in patients with alcoholism.[5] If treated patients drink alcohol, they have a more severe "acetaldehyde syndrome," characterized by intense palpitations, throbbing headache, nausea and vomiting, weakness, and vertigo. Disulfiram use discourages drinking but does not cure alcoholism.[6]

Intoxication

Ethanol readily crosses the blood-brain barrier, and consequently, brain and blood alcohol concentrations equilibrate rapidly after drinking. Intoxication develops in nonalcoholic persons at blood alcohol levels of 10 to 35 mmol per liter (50 to 150 mg per dl) and is more severe when blood levels are rising.[3] There is usually euphoria, a loss of social inhibitions, and garrulous behavior, but sometimes intoxicated people are gloomy and belligerent. Some do not experience euphoria but only become drowsy; they rarely abuse alcohol. At higher blood ethanol concentrations, cerebellar and vestibular function deteriorates, and lethargy and stupor may supervene. In nonalcoholic persons, blood ethanol concentrations of

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ABBREVIATIONS USED IN TEXT

cyclic AMP = adenosine 3′:5′-cyclic phosphate
GABA = γ-aminobutyric acid
5-HT_3 = 5-hydroxytryptamine$_3$
LS = long sleep [mouse line]
MAO = monoamine oxidase
MRI = magnetic resonance imaging
NMDA = *N*-methyl-D-aspartate
SS = short sleep [mouse line]

110 mmol per liter (500 mg per dl) can be fatal, usually because of respiratory depression and hypotension. Persons with alcoholism are more resistant to ethanol intoxication than nonalcoholic persons.[7-10]

Alcoholic "blackouts" can occur during heavy drinking and are characterized by hours of amnesia while awake. Immediate recall and long-term memory are normal, but new events are forgotten, as in patients with transient global amnesia. Although alcoholic blackouts have been related to reduced plasma tryptophan levels,[11] ethanol inhibition of *N*-methyl-D-aspartate (NMDA) receptor-stimulated calcium flux in the hippocampus may be more important.[12-15]

Tolerance

Tolerance to alcohol can be acute or chronic. "Acute tolerance" to alcohol develops rapidly[3,16]; after drinking several hours, a person can appear to be sober at blood alcohol levels that caused intoxication earlier.[17] "Chronic tolerance" is a characteristic feature of alcoholism, and alcoholic persons can appear sober at blood alcohol concentrations of 90 to 110 mmol per liter (400 to 500 mg per dl).[9] The highest recorded level is 330 mmol per liter (1,510 mg per dl) in an ambulatory person with chronic alcoholism who had stopped drinking three days earlier.[8] Tolerance is caused by adaptive molecular changes in the brain.

Alcohol Withdrawal Syndrome

When drinking is abruptly reduced or discontinued, a hyperexcitable withdrawal syndrome develops that is considered to be evidence of "physical dependence."[18] Clinical features include tremulousness, disordered perceptions, convulsions, and delirium tremens.[16] These symptoms and signs appear to be due to adaptive neural mechanisms that are no longer opposed by the depressant effects of ethanol.

Tremor is a common symptom, beginning six to eight hours after the last drink and worsening in one to two days. Sympathetic hyperactivity with elevated levels of norepinephrine and its metabolites has been documented,[19] and treatment with sympatholytic drugs can be helpful.[20,21] The calming effects of benzodiazepines, however, are more effective.

Disordered perceptions may parallel the development of tremor and sympathetic hyperactivity, becoming most pronounced at 24 to 36 hours and clearing in a few days. Ordinary visual, auditory, and sensory experiences become distorted and misinterpreted. Vivid nightmares interfere with sleep. Auditory hallucinations ("alcoholic hallucinosis") can persist for weeks, even though other manifestations of ethanol withdrawal have abated. The goal of treatment with benzodiazepines is to suppress symptoms and produce mild sedation.

Generalized tonic-clonic convulsions can develop within one to two days after reducing or stopping drinking.[16] Multiple seizures are common and usually occur over 6 to 12 hours; status epilepticus is unusual. Some attribute the development of seizures to ethanol intoxication, not withdrawal.[22] But ethanol dependence is followed by withdrawal seizures in animals, and mice have been bred in the laboratory to have convulsions on ethanol withdrawal.[23] Phenytoin is not useful in managing alcohol withdrawal seizures,[24] but sedating doses of benzodiazepines are effective.[25] Calcium channel antagonists may prove to be beneficial,[26,27] but further study is needed.

Agitation, global confusion, insomnia, frightening hallucinations, and sympathetic hyperactivity characterize delirium tremens. These alarming manifestations develop abruptly several days after the occurrence of tremors and generalized hyperexcitability. This is a serious disorder, and associated electrolyte abnormalities, hyperthermia, and dehydration with circulatory collapse can be fatal. Therapy includes fluid replacement, the correction of associated electrolyte disorders such as hypokalemia and hypomagnesemia, and sedation with benzodiazepines.

Cellular Pathophysiology of Ethanol Intoxication, Tolerance, and Physical Dependence

Acute and chronic ethanol-induced changes in membrane-dependent events appear to be related to acute intoxication, tolerance, and physical dependence. Ethanol intercalates into cell membranes,[28] increasing membrane fluidity,[29] but it is not clear how changes in membrane order control physiologic function.[30] Recent evidence suggests that proteins involved in signal transduction may be more important pathophysiologic targets for alcohol. Components of signal transduction cascades that adapt to ethanol include ion channels,[31-34] second messengers,[35-39] neurotransmitters and their receptors,[15,40-43] G proteins,[44-46] chaperonins,[47] and regulators of gene expression.[47,48]

γ-Aminobutyric Acid Receptors

γ-Aminobutyric acid (GABA) is the predominant inhibitory neurotransmitter in the brain. Two types of GABA receptors have been described, $GABA_A$ and $GABA_B$. $GABA_A$ receptors are hetero-oligomeric protein complexes that contain a chloride ionophore and have specific allosteric binding sites for benzodiazepines and barbiturates.[49] Intoxicating concentrations of ethanol (5 to 50 mmol per liter [22 to 220 mg per dl]) increase chloride flux through $GABA_A$-receptor-operated chloride channels, and this effect is blocked by the GABA antagonists, bicuculline and picrotoxin.[41,50]

Selected lines of mice and rats have been used to detect genetic differences in $GABA_A$ receptors that may contribute to differences in behavioral responses to

ethanol. The "long-sleep" (LS) and "short-sleep" (SS) mouse lines were selected for differential sensitivity to the hypnotic effect of ethanol.[51] Chloride 36-flux in membrane vesicles made from LS mice is more sensitive to enhancement by ethanol and benzodiazepines than in vesicles from SS mice. Similar results have been found in other rodent lines, all suggesting a strong association between in vivo ethanol intoxication and in vitro inhibition of chloride flux by ethanol. These differences in $GABA_A$-activated chloride channel function are maintained when $GABA_A$ receptors are expressed in *Xenopus laevis* oocytes using messenger RNA from brains of LS and SS mice.[52] The biochemical basis for these differences in $GABA_A$ receptors from LS and SS mice is not yet known.

Several genes encoding subunits for the $GABA_A$-receptor complex have now been cloned. At least six different α clones, three β sequences, two γ subtypes, and one δ clone have been described.[49,53,54] The γ2 subunit exists as alternatively spliced short (γ2s) and long (γ2l) forms, the latter containing 24 additional nucleotides that encode a phosphorylation site for protein kinase C on an intracellular loop.[55] Recent evidence from studies of messenger RNA expression in *X laevis* oocytes indicates that the γ2l subunit is required for ethanol potentiation of $GABA_A$-receptor activation.[56]

Benzodiazepine inverse agonists, such as the imidazobenzodiazepine Ro15-4513, prevent the intoxicating, antianxiety, and anticonvulsant effects of ethanol in rodents and antagonize ethanol enhancement of agonist-stimulated chloride flux through $GABA_A$ receptors.[41,50,57,58] Thus, it may be possible to design safe drugs that modulate $GABA_A$-receptor function to block the acute intoxicating effects of ethanol in humans.

Calcium Channels

Ethanol-induced changes in calcium channels may account for some of the signs and symptoms of ethanol withdrawal. Exposure to ethanol for several days increases depolarization-stimulated calcium chloride Ca 45 uptake.[33,59] Calcium flux remains elevated for several hours after the removal of ethanol[33,59] and is associated with an increase in the number of binding sites for dihydropyridine calcium channel antagonists.[33,59,60] Increases in dihydropyridine-sensitive calcium channels could induce withdrawal symptoms by promoting neurotransmitter release.[61] The importance of calcium channels in the pathogenesis of alcohol withdrawal syndromes is supported by evidence that calcium channel antagonists reduce the incidence of tremors, seizures, and death in alcohol-dependent mice and rats deprived of ethanol[27,62] and reduce withdrawal symptoms in patients with alcoholism.[26] Ethanol-induced stimulation of dihydropyridine binding sites is much greater in mice selectively bred for severe alcohol withdrawal seizures than in mice bred for mild signs of alcohol withdrawal.[63] Therefore, the magnitude of alcohol withdrawal may be regulated by genetic factors that control the expression of dihydropyridine-sensitive calcium channels.

Excitatory Amino Acids

In the nervous system, glutamate, aspartate, and their structural analogues bind to receptors that regulate ion channels or activate phosphoinositide hydrolysis.[64] Specific receptors respond to the excitatory amino acid agonists, NMDA, kainate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, or L-2-amino-4-phosphonobutanoic acid, but the NMDA receptor is particularly sensitive to ethanol. Intoxicating concentrations of ethanol (5 to 50 mmol per liter) inhibit NMDA-activated calcium currents in rat hippocampal neurons[13] and dorsal root sensory neurons[15] and reduce NMDA-stimulated calcium uptake in cerebellar granule cells.[12] Intoxicating concentrations of ethanol also inhibit cellular responses to NMDA-receptor activation, including neurotransmitter release,[65] cyclic guanosine monophosphate production,[12] and the generation of excitatory postsynaptic potentials.[14] *N*-Methyl-D-aspartate receptors are important for long-term synaptic potentiation, which appears to play an important role in learning and memory.[66] Thus, ethanol inhibition of NMDA receptors may explain cognitive defects and "blackouts" associated with intoxication and binge drinking.[12]

Long-term exposure to ethanol causes an increased expression of glutamate receptors in the brains of alcoholic humans and synaptosomes from rats administered ethanol for two to three weeks.[67,68] Recent evidence suggests that the increases also contribute to the generation of alcohol-withdrawal seizures.[69]

Dopamine and Serotonin

Dopamine is implicated in neural mechanisms of reward, reinforcement, and craving, and psychoactive drugs, including ethanol, increase dopamine release from mesolimbic regions in rats.[70] 5-Hydroxytryptamine$_3$ (5-HT_3) receptors control dopamine release,[71] and in mesolimbic regions, dopamine release induced by ethanol is blocked by 5-HT_3 antagonists.[72,73] Ethanol potentiates 5-HT_3-receptor activation,[74] and 5-HT_3-receptor antagonists reduce ethanol intake[75] and the ability to discriminate between water and alcohol. These findings suggest that serotonin, acting at 5-HT_3 receptors, may mediate some aspects of ethanol intoxication and ethanol-seeking behavior.

Adenosine Transporters, A_2 Receptors, and Adenosine 3′:5′-Cyclic Phosphate Production

Adenosine is an inhibitory neuromodulator in the nervous system. Adenosine modulates calcium channels, the release of neurotransmitters, and the activation of neurotransmitter receptors.[76,77] Recent evidence suggests that adenosine may mediate many of the effects of ethanol in the brain.[42,78-81] Acute ethanol exposure inhibits adenosine uptake by a specific kind of nucleoside transporter.[82] This causes an accumulation of extracellular adenosine,[79,80] which activates adenosine A_2 receptors, thereby increasing the levels of adenosine 3′:5′-cyclic phosphate (cyclic AMP).[35,36,83] With prolonged ethanol exposure, increases in cyclic AMP are usually followed by adaptive desensitization of cyclic-AMP production.[36] This appears to be a "heterologous desensitization" of receptors coupled posi-

tively to adenylyl cyclase by the stimulatory G protein, G_S.[45] Such cells require ethanol to maintain normal levels of cyclic AMP,[36] and thus they represent an example of physical dependence on ethanol at a cellular level. Ethanol-induced heterologous desensitization appears to be due primarily to a decrease in messenger RNA for $G\alpha_S$,[45] the guanosine triphosphate-binding component of G_S. This causes a reduction in $G\alpha_S$ protein[44,45] and decreases functional coupling between receptors and adenylyl cyclase.[45] Under these conditions, the adenosine transporter loses its sensitivity to ethanol inhibition, presumably because of reduced cyclic AMP-dependent protein kinase A activity. Thus, in naive cells, adenosine uptake is inhibited by acute ethanol exposure, but uptake becomes insensitive to ethanol inhibition after long-term ethanol exposure.[80] This is an example of "chronic tolerance" to ethanol at a cellular level.

The pathophysiologic importance of altered adenosine regulation and desensitization of cyclic AMP production is suggested in studies of circulating lymphocytes from actively drinking alcoholic persons. Cells from patients with alcoholism show a striking reduction in cyclic-AMP levels and a desensitization of adenosine-stimulated cyclic-AMP production.[35] In addition, nucleoside transport appears to be altered in actively drinking alcoholic persons as their blood cells are resistant to the inhibition of adenosine uptake by ethanol (discussed later). It may be anticipated that adenosine receptor antagonists acting at specific sites in the brain could prevent many of the acute and chronic effects of ethanol on cyclic-AMP signal transduction and, perhaps, prevent acute intoxication and physical dependence.

Genetic Studies of Alcoholism

Considerable evidence exists that genetic factors play a role in alcoholism. Alcoholism is about seven times more frequent in first-degree relatives of alcoholic persons than in the general population.[84] In addition, 16% to 26% of fathers and 2% to 6% of mothers of alcoholic persons also have alcoholism.[84] Identical twins have a significantly higher concordance of alcoholism than fraternal twins, even when environmental factors, such as the greater frequency of social contact between identical twins, are taken into account.[85,86] The strongest evidence for heritability of alcoholism has come from adoption studies. Among alcoholic patients with severe alcohol-related behavioral or medical complications, adoptees have an average of 2.5 times greater chance of alcoholism developing if at least one biologic parent had alcoholism.[84]

Based on the results of Swedish adoption studies, Cloninger described two subtypes of alcoholism.[87] Type 1 is more common among men and women with female alcoholic relatives, whereas the type 2 syndrome is characteristic of male relatives of alcoholic men. Those with type 1 alcoholism tend to drink excessively later in life, usually after an extended period of social drinking. They can abstain from alcohol or engage in binge drinking. Associated personality traits in type 1 alcoholism include anxiety, high reward dependence, emotional dependence, rigidity, and perfectionism. Type 2 alcoholism is associated with antisocial personality traits such as impulsivity, fighting, drunk driving, and criminal behavior. Persons with type 2 alcoholism begin drinking in their teens or early adulthood, actively seek alcohol, and usually cannot abstain from drinking. Whether this classification scheme will prove to be useful in clinical and genetic studies remains to be determined.[88]

Linkage Analysis of Alcoholism

Studies linking alcoholism with the chromosome 4q blood group marker MNS and the esterase D marker on chromosome 13q have been reported,[89,90] but these results are inconclusive for substantial linkage. Recently a complementary DNA probe, which contains the last coding exon of the dopamine D_2-receptor gene and 16.5 kilobases of the noncoding sequence on chromosome 11, has been used to examine brain tissue from 35 persons with and 35 without alcoholism.[91] These results provided statistical evidence for the presence of a genetic locus of susceptibility to a severe form of alcoholism in the q22-q23 region of chromosome 11. Several authors have criticized the criteria used for retrospectively diagnosing alcoholism in this study and have warned against overinterpreting the results from such a limited number of patients.[92-94] Moreover, a subsequent study of 40 living, unrelated persons with alcoholism and two families with multigenerational alcoholism failed to confirm this linkage.[95] Clearly, much work is necessary to identify the gene(s) involved in alcoholism. This is likely to be a formidable problem because the contribution of a specific genotype will be complicated by the heterogeneity of alcoholism and the absence of precise diagnostic criteria. For example, in families with a history of alcoholism, some individuals with genetic risk might choose never to drink, while others without genetic risk might become alcoholic because of socioeconomic reasons. Therefore, even if a probe for a linked gene were used in linkage studies in families, it might not be possible to achieve a significant lod score because of the heterogeneity of alcoholism. Multigenic approaches may prove to be more valuable. Also, it may be more plausible to search for phenotypic biochemical or molecular markers of alcoholism. Once a candidate phenotype is recognized, it should be possible to identify specific genes involved in alcoholism.

Possible Phenotypic Markers of Genetic Alcoholism

Behavioral and Neurophysiologic Markers

Subjective and objective measurements of intoxication can be correlated with blood alcohol concentrations so that the sensitivity of neurologic responses to alcohol can be studied for a genetic linkage to alcoholism.[96] In studies of subjects whose parents had alcoholism, a reduced sensitivity to ethanol is suggested, but a definitive genetic marker has not been identified. Neurophysiologic studies may be more promising. Changes in electroencephalographic activity and sensory-evoked responses have been reported in the offspring of alcoholic persons,

and the amplitude of the P300 component of event-related brain potentials may be reduced in young sons of persons with alcoholism.[97,98]

Biochemical Markers

Numerous studies have documented decreased levels of platelet monoamine oxidase (MAO) activity in alcoholic persons.[99] Low MAO activity may be more common in alcoholic persons and those who abuse mixed drugs who have personality traits consistent with type 2 alcoholism.[100,101] There is much overlap between individual patients and controls, however, and MAO activity in alcoholic patients fluctuates with abstinence, suggesting that decreases in MAO activity result from alcohol exposure. Ethanol inhibits platelet MAO activity, and inhibition is greater in platelets from alcoholic subjects than from controls.[102] This difference does not appear to be associated with the duration of abstinence from alcohol, suggesting that ethanol inhibition of MAO activity may involve inherited factors.

Freshly isolated lymphocytes from alcoholic persons who drink heavily show a 76% reduction in basal and receptor-stimulated cyclic-AMP levels when compared with age- and sex-matched controls and patients with nonalcoholic liver disease.[35] Subsequent studies in platelet membranes from alcoholic patients have also shown a reduction in prostaglandin E_1-stimulated cyclic-AMP levels.[102] Freshly isolated lymphocytes from heavily drinking patients with alcoholism show a desensitization of adenosine receptor-dependent cyclic-AMP production[83] that mimics changes produced by adding ethanol to neural cells in culture.[36,45] When lymphocytes from alcoholic subjects and controls were cultured for seven to eight days in the absence of ethanol, the cells from alcoholic persons recovered and basal cyclic-AMP levels were the same as controls. When these same lymphocytes were administered adenosine, they showed a 2.8-fold greater stimulation of cyclic-AMP production than did lymphocytes from nonalcoholic subjects.[83] In addition, lymphocytes from alcoholic subjects were more sensitive to ethanol than cells from nonalcoholic subjects. After ethanol treatment for 24 hours, lymphocytes from alcoholic subjects exhibited desensitization of cyclic-AMP signal transduction, whereas cells from nonalcoholic persons showed no change under the same conditions.[83] Because these differences were observed after four to six cell divisions in the absence of ethanol, they may reflect genetic differences between alcoholic and nonalcoholic subjects.

Freshly isolated lymphocytes from alcoholic subjects also exhibit abnormal lipid metabolism. Ethanol is an exogenous substrate for phospholipase D, leading to the accumulation of phosphatidylethanol.[103-105] Lymphocytes from alcoholic patients show increased synthesis of phosphatidylethanol[105]; it is not known whether this is due to genetic factors or to continued exposure to ethanol.

Alcohol-Related Neurologic Disorders

With prolonged drinking, there is a curious transition between reversible metabolic effects of ethanol and the development of organ damage in the brain and elsewhere. Some propose that malnutrition is the cause of most alcohol-related neurologic disorders.[106] People with alcoholism often obtain as much as 50% of their calories from ethanol, and serious nutritional deficiencies can develop, particularly for protein, thiamine, folate, and niacin. On the other hand, studies of well-nourished alcoholic patients with skeletal and cardiac alcoholic myopathy suggest that a lifetime threshold of ethanol consumption is exceeded before irreversible muscle damage occurs.[107] In addition, recent evidence suggests that genetic factors contribute to the diverse toxicity of ethanol.[108] Ethanol can also be an exogenous substrate for specific enzymes leading to the accumulation of possibly toxic abnormal products. These include phosphatidylethanol[103-105] and fatty-acid ethyl esters.[109,110] In addition, acetaldehyde is a possible toxin. Acetaldehyde can react with diverse proteins to form acetaldehyde-protein adducts that accumulate in proportion to the amount of ethanol consumed during chronic alcoholism.[111,112] Prolonged ethanol-induced changes in receptor-stimulated second messenger production and ion-channel function could also be cytotoxic, particularly for organs with little cell turnover, such as brain, muscle, and liver.

Wernicke's Encephalopathy and Korsakoff's Psychosis

Wernicke's encephalopathy is caused by thiamine deficiency[113,114] and is characterized by the triad of ataxia, oculomotor abnormalities, and global confusion. On microscopic examination, demyelination, necrosis, gliosis, and vascular proliferation occur in the mamillary bodies, superior cerebellar vermis, hypothalamic nuclei, and other gray matter regions of the diencephalon and brain stem. Most patients have chronic alcoholism, but cases associated with persistent vomiting, starvation, renal dialysis, iatrogenic malnutrition, and malignant neoplasms have also been reported. Therefore, Wernicke's encephalopathy should be suspected in any poorly nourished patient with altered mental status.

Because cerebellar lesions are most severe in the superior vermis, patients usually have gait ataxia with few signs of limb incoordination. Nystagmus is the most common ocular sign. Bilateral rectus palsies and horizontal conjugate defects are also common. Vertical gaze palsies occur less frequently, and complete ophthalmoplegia is rare. Other infrequent findings include ptosis, internuclear ophthalmoplegia, and loss of pupillary reflexes.

The acute confusional state is characterized by inattention, disorientation, and sleepiness. Sometimes patients are agitated, but most are apathetic, indifferent, and amnestic. Impaired consciousness can be an important feature in otherwise unrecognized cases of Wernicke's encephalopathy, so that this diagnosis must be considered in all patients with unexplained stupor and coma. In addition to the classic triad, patients may have hypotension or hypothermia due to hypothalamic involvement. Most patients have associated polyneuropathy (discussed later).

In alcoholic patients, thiamine deficiency may result from an inadequate diet, impaired intestinal absorption, and decreased hepatic thiamine storage.[115] Four enzymes involved in intermediary metabolism require thiamine pyrophosphate as a cofactor: pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, transketolase, and branched-chain α-ketoacid dehydrogenase. The affinity of transketolase for thiamine is reduced in some patients with Wernicke's encephalopathy.[116,117] These patients are at greater risk for functional thiamine deficiency to develop when thiamine levels in the diet are marginal.

Autopsy studies indicate that Wernicke's encephalopathy is much more prevalent than recognized during life. Although the diagnosis is usually made on clinical grounds, computed tomography and magnetic resonance imaging (MRI) may aid in diagnosing mild or atypical cases.[118,119] The volume of the mamillary bodies is reduced in chronic Wernicke's encephalopathy. Calculating the volume of the mamillary bodies by MRI can distinguish patients with Wernicke's encephalopathy from unaffected controls or patients with Alzheimer's disease.[118]

If the disease is untreated, the mortality rate is 10% to 20%. Diagnosis is critical because treatment usually corrects most or all of the abnormalities. Because patients are at risk for cardiovascular collapse, Wernicke's encephalopathy must be considered a medical emergency. Patients should be admitted to a hospital and thiamine, 100 mg per day for several days, administered parenterally to ensure absorption. It is important to begin therapy before feeding or administering parenteral glucose solutions because carbohydrates can precipitate or worsen the encephalopathy. Outpatient therapy should continue with at least 50 mg of thiamine per day because thiamine absorption is often impaired in patients with alcoholism. With treatment, ocular abnormalities may resolve within hours to a few days; confusion and ataxia usually resolve more slowly.

Sequelae include gait ataxia, nystagmus, and Korsakoff's psychosis. Korsakoff's psychosis is a chronic amnestic disorder that occurs in most patients who survive Wernicke's encephalopathy.[114,120] Remote memories remain intact, but there is retrograde amnesia for recent memories, and patients are usually disoriented to place and time. Particularly striking is an inability to learn new information (anterograde amnesia). Immediate recall is intact, but patients are unable to remember the same information several minutes later. They appear to be unaware of their deficit, and confabulation is common. Alertness and other aspects of cognitive function are unaffected. Lesions in the dorsal medial nuclei of the thalamus are probably responsible for the memory deficits.[121] About 25% of patients never recover and require long-term care, whereas 20% recover completely over several months.[113] It is not clear whether thiamine is effective in treating Korsakoff's syndrome.

Alcoholic Cerebellar Degeneration

A cerebellar syndrome occurs in some patients with alcoholism. It is characterized by gait ataxia with lesser degrees of limb ataxia affecting the legs more than the arms.[114] The syndrome occurs after several years of alcoholism and usually develops gradually. There is loss of cerebellar cortical neurons, particularly in the anterior and superior vermis, and less often in the anterior and superior cerebellar hemispheres. Because this is similar to cerebellar lesions seen in Wernicke's encephalopathy, some clinicians attribute alcoholic cerebellar degeneration to thiamine depletion. The disorder may also result from a direct toxic effect of alcohol or from electrolyte derangement.[122] The development of cerebellar degeneration does not correlate with the amount of alcohol consumed,[123] and affected patients appear to drink less than other alcoholic persons. This suggests that cerebellar damage may develop in some alcoholic persons because of genetic vulnerability. Cerebellar dysfunction frequently abates or stabilizes with abstinence and improved nutrition.[124]

Alcoholic Dementia

Cognitive deficits attributed to a neurotoxic effect of ethanol frequently develop in persons with alcoholism; this observation is supported by experimental and histologic data. Several studies have provided evidence for a direct neurotoxic effect of ethanol on the brain. In rodents, long-term ethanol consumption causes learning deficits, altered dendritic structure, and a loss of neurons.[125] Courville first described neuropathologic changes in alcoholic persons with dementia, including cortical atrophy, enlargement of the lateral ventricles, and a loss of cortical neurons.[126] Lynch examined the brains of 11 persons with alcoholism and described a patchy loss of cortical neurons.[127] In quantitative autopsy studies, a statistically significant loss of brain tissue and a loss of cortical neurons were found, especially in frontal cortex, in alcoholic patients.[128,129] Some authors have argued that such findings are nonspecific or artifactual and that unrecognized Korsakoff's syndrome accounts for most cases of mental impairment among alcoholic persons.[114,130]

Computed tomographic and MRI studies have shown symmetrical enlargement of lateral ventricles, increased size of cerebral sulci, and increases in the width of interhemispheric and sylvian fissures in alcoholic patients. In addition, patients with alcoholism commonly have cognitive deficits on psychometric tests. Radiographic changes and psychological test performance may improve if drinking is discontinued, suggesting that cerebral atrophy and cognitive deficits are partially reversible.[131] Reversible atrophy may be due to alterations in dendritic structure that are reversed by abstinence in rats with long-term exposure to ethanol.[132] Other disorders that cause impaired cognitive function in persons with alcoholism include thiamine deficiency, pellagra, hepatocerebral degeneration, recurrent head trauma, and Marchiafava-Bignami disease.

Central Pontine Myelinolysis

Central pontine myelinolysis is an uncommon disorder found most often in alcoholic patients. Hyponatremia frequently precedes this disorder, and aggressive correc-

tion of chronic hyponatremia appears to be the major precipitating factor in humans and animals.[2] Characteristically, there is bilaterally symmetrical, focal destruction of white matter in the ventral pons, and about 10% of patients have extrapontine lesions in the thalamus, basal ganglia, cerebellum, and cerebral white matter. The lesions exhibit a loss of myelin and a reduced number of oligodendroglia, with relative sparing of neurons and axons and no inflammation or vascular changes.

Typically central pontine myelinolysis evolves over days to weeks. Mental confusion is prominent. Demyelination of pontine corticobulbar fibers may lead to dysarthria, mutism, dysphagia, facial and neck weakness, conjugate gaze palsies, and impaired tongue movement. Corticospinal tract lesions in the pons produce paraparesis or quadriparesis. In severe cases a "locked-in" syndrome may develop.

The cerebrospinal fluid is normal or may show elevated pressure and increases in protein, including myelin basic protein. Brain-stem auditory evoked potentials may be abnormal and improve as the patient recovers. Magnetic resonance imaging is more sensitive than computed tomography for detecting pontine lesions.[133] Patients with central pontine myelinolysis should be supported vigorously because they can improve after several weeks.[134]

Alcoholic Neuropathy

Polyneuropathy is the most common neurologic complication in alcoholism. Patients report paresthesias, pain, and weakness, especially in the feet. Dysesthesias can be so severe that they interfere with walking. Examination reveals reduced pain and temperature sensation. Distal muscle weakness and atrophy are common, greater in the legs than in the arms. Deep tendon reflexes are reduced, and ankle reflexes are usually absent, even in asymptomatic patients. Cerebrospinal fluid protein levels are usually normal or slightly elevated.

Alcoholic polyneuropathy is characterized by axonal degeneration and demyelination. Although earlier clinical evidence suggested that inadequate nutrition was responsible,[106] a specific vitamin deficiency has never been documented. Recent evidence suggests a direct neurotoxic effect of ethanol on peripheral nerves.[135,136] Alcoholic persons frequently suffer entrapment or pressure neuropathies, particularly of ulnar and peroneal nerves.[137] Recovery in abstinent patients is slow and often incomplete, requiring weeks to months.

Alcoholic Myopathy

Acute alcoholic myopathy is a dramatic and life-threatening disorder that can develop after several days of heavy binge drinking.[138] Patients experience pain, cramps, tenderness, proximal weakness, and swelling of the muscles, sometimes associated with cardiac arrhythmias. Blood creatine kinase levels are elevated, associated with rhabdomyolysis and myoglobinuria. This frequent complication may lead to hyperkalemia, renal failure, and death. Recovery usually occurs within days to weeks of abstinence, but residual weakness in proximal muscles may remain.

Chronic alcoholic myopathy is usually a painless syndrome of proximal muscle weakness and atrophy that is not often recognized. Nearly 50% of asymptomatic persons with alcoholism probably have a skeletal myopathy.[107] Myopathy can be mild or severe, and coexistent alcoholic peripheral neuropathy may contribute to the weakness. Alcoholic skeletal myopathy and alcoholic cardiomyopathy have been reported to develop simultaneously in well-nourished alcoholic persons, and there is a direct relationship between the amount of ethanol consumed and the severity of the myopathies.[107] Improvement usually occurs two to three months after discontinuing drinking. Repeated ethanol administration to human volunteers for 28 days causes muscle damage despite adequate nutrition, indicating that myopathy results from ethanol toxicity and not nutritional factors.[139] Current concepts suggest that myopathy is due to direct toxicity of ethanol, acetaldehyde, or other ethanol metabolites.[107,138]

Summary

Research on alcoholism is ready to benefit from major advances in molecular genetics and cell biology that are fueling a revolution in the diagnosis and treatment of disease. Alcohol-induced changes in gene expression and signal transduction probably mediate alcohol tolerance, dependence, and neurotoxicity. In addition, inherited factors appear to regulate drug-seeking behavior, the development of tolerance to alcohol, and susceptibility to the neurotoxic effects of alcohol. The discovery of genes that confer risk for alcoholism and alcohol toxicity, and understanding fundamental alcohol-induced changes in gene expression and cellular function, will make it possible to design new therapies to prevent or ameliorate alcoholism and alcoholic neurologic disorders.

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Stroke
Revolution in Therapy

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Stroke remains the third leading cause of death in this country, although recent advances in both clinical and basic science research have revolutionized the concept of stroke. Studies of primary and secondary stroke prevention have now documented the means to prevent thousands of cases of stroke each year. Three distinct strategies are evolving for intervention in the acute stroke process. Evidence is clear that ischemia leads to a toxic accumulation of intracellular calcium, in part mediated by excitatory neurotransmitters such as glutamate. Glutamate antagonists have shown clear benefit in experimental stroke models, and early clinical trials are underway. Acute revascularization to restore perfusion is also feasible and may minimize the extent of infarction. Studies of fibrinolytic agents are promising, with randomized clinical studies being done. While reperfusion is desired, it may be associated with additional neuronal injury. The development of anaerobic metabolism followed by reperfusion and aerobic conditions favors oxidation and free-radical formation. This mechanism of injury can be decreased by agents known to scavenge free radicals, and clinical trials are also testing this. This revolution in the understanding of ischemia, as well as the outpouring of new pharmacologic agents, is making stroke a true neurologic emergency requiring immediate intervention.

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Stroke remains the third leading cause of death in this country, with approximately 500,000 new events per year. Modern clinical research techniques have been applied to cerebrovascular disease, and the recent advances in stroke prevention have been profound. The importance of stroke prevention is underscored by the history of frustrated attempts at acute stroke therapy. Primary prevention studies of long-term warfarin anticoagulation in patients with cardiac risk factors for embolic stroke such as atrial fibrillation have clearly demonstrated the efficacy of anticoagulation.[1-3] Thousands of cases of embolic strokes can now be prevented, with profound benefits in spared morbidity. Likewise, recent advances have occurred in the secondary prevention of stroke in patients with symptomatic and severe carotid stenosis.[4,5] Surgical endarterectomy can be a powerful intervention to prevent stroke and improve outcome.

Yet intervention in cases of acute stroke remains the challenge, and it is in this area that vast efforts are focused. New information about brain ischemia and clinical stroke has revolutionized the conceptualization of the process from the onset of symptoms to the eventual neurologic outcome. This information also allows the development of logical strategies for intervening in the process. Three distinct strategies have emerged with efforts to effect neuronal protection against ischemia, urgently revascularize and restore perfusion, and block the cascade of reperfusion injury (Figure 1).

In discussions of acute stroke intervention, it is most important to define clearly the concepts involved. Stroke and transient ischemic attack are best viewed as clinical terms to describe the sudden occurrence of neurologic deficits related to cerebral ischemia. Infarction relates to tissue death and necrosis defined at microscopic examination and inferred from x-ray films. Stroke has been arbitrarily differentiated from transient ischemic attack as the term applied to ischemic deficits that persist more than 24 hours. This differentiation supports the concept of reversible ischemia, but it must be emphasized that this term is distinct from the concept of the presence or absence of infarction. Clearly, some events called transient ischemic attacks by this clinical definition will have infarction demonstrated by computed tomography or magnetic resonance imaging studies.

Various vascular mechanisms underlie stroke. Most are thought to be thromboembolic, with the heart or carotid arteries as common sources. Many cases of embolic stroke, however, have no readily identifiable source despite a thorough clinical investigation. Perhaps 10% of stroke cases result from small-vessel disease, leading to subcortical lacunar infarction most often in association with hypertension or diabetes mellitus. An additional

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ABBREVIATIONS USED IN TEXT

NMDA = *N*-methyl-D-aspartate
tPA = tissue plasminogen activator

10% to 20% result from intracranial vascular disease and low-flow states where proximal occlusive disease occurs without adequate collateral pathways. Taken as a whole, stroke represents a wide spectrum of clinical deficits with varying underlying vascular pathophysiology. This clinical heterogeneity must be accounted for when considering therapy for acute stroke.

Acute stroke should be viewed as a dynamic and evolving process. Although from clinical observation the stroke deficit often occurs suddenly and may be complete at its onset, the underlying tissue ischemia leading to infarction is a dynamic process that evolves over time. Tissue can be rendered nonfunctional yet have the potential for recovery if the ischemia can be tolerated or reversed. Evidence does exist for the notion of a dynamic and reversible ischemic process. Positron-emission tomographic studies have provided a glimpse into the process of acute stroke evolution. This technology is able to measure cerebral oxygen metabolism, blood flow, and therefore an oxygen extraction fraction. Increases in the oxygen extraction fraction indicate impaired oxygen delivery with continued oxygen metabolism. In many cases of stroke, there is a central core of tissue with such profound impairment of oxygen delivery that oxygen metabolism ceases and infarction rapidly occurs. There is also commonly an area surrounding the core where the impairment of oxygen delivery is less profound and marginal oxygen metabolism can continue for some time. Serial positron-emission tomographic examinations have established that some portions of tissue are profoundly ischemic and infarction ensues, while other portions are ischemic with compromised oxygen metabolism, but they survive and recover. It is important to emphasize that this process evolves over hours and likely varies greatly from case to case, depending on the anatomy of vascular collaterals and the duration of vascular occlusion. Substantial studies of experimental stroke in animals and limited clinical studies have documented the concept of a "therapeutic window" during which tissue may be "salvaged." The time interval for efficacious intervention in stroke patients has not been clearly defined, but most efforts have been aimed at intervention within six hours of the onset of symptoms.

Neuronal Protection

One strategy for acute stroke intervention is to protect neurons from ischemic insult. The susceptibility of various neurons to transient ischemia differs considerably. Some may die within hours, while others appear unaffected. Hippocampal neurons are particularly sensitive to ischemia, and it has also been shown that sensitivity to the effects of excitatory neurotransmitters such as glutamate follows a similar pattern.[6] Ischemic insult leads to a cascade of events, including neuronal depolarization and an accumulation of intracellular calcium that may eventually lead to ischemic cell death.[7] Much evidence supports the "glutamate hypothesis" or "excitotoxin hypothesis" of cerebral ischemia.[8-10] This hypothesis suggests that ischemia leads to accumulations of high concentrations of glutamate and other excitatory amino acid transmitters in the synaptic clefts opening calcium channels leading to excessive calcium influx. This overwhelming calcium assault leads to eventual neuronal death. Extensive in vitro work has demonstrated the toxic effect of glutamate and glutamate analogues and the ability to block that toxic effect with glutamate antagonists.[11]

In animal stroke models, glutamate receptor antagonists have been studied with variable results. Agents that block the glutamate-activated *N*-methyl-D-aspartate (NMDA) channel have been extensively studied. Studies in animals with experimentally induced stroke have clearly shown the increased complexities of ischemia in vivo. Although some early beneficial results in a global ischemia model may have related to alterations in brain temperature as much as to any calcium effect,[12] overall the glutamate hypothesis remains a viable concept for manipulating neuronal ischemic injury. Many agents are emerging from laboratory efforts, with promising data in experimental stroke models. Models of focal ischemia may most closely mimic clinical stroke, and infarct volume reductions are consistently demonstrated in studies with NMDA antagonists. Early clinical trials in patients with acute stroke are currently underway with some of these agents. The goal of these studies will be to identify agents that improve neurologic outcome, presumably by providing neuronal protection against ischemia. For clinicians this strategy opens a new era in patient care.

Acute Revascularization

Stroke most often occurs as a result of acute vascular occlusion, and therefore acute revascularization represents a clear and logical extension of the pathophysiologic mechanism. The source of this embolic material is generally felt to be thrombus originating at a more proximal site. Angiographic studies in patients with acute stroke demonstrate appropriate vascular occlusion in as much as 80% of cases when studies are done in the first hours, with findings falling to 20% by 24 hours. The endogenous lytic system is likely involved in breaking down the obstruction, and the natural history of stroke ultimately is reperfusion. Prompt revascularization to restore perfusion may minimize the extent of infarction and improve neurologic outcome. Neurologists have had an interest in acute revascularization for some time. Early work with thrombolytic agents was carried out in the 1960s and 1970s using intravenous urokinase and streptokinase.[13,14] These early clinical studies enrolled patients at varying time intervals after symptoms began and were hampered by a lack of imaging techniques to accurately differentiate infarction from primary hemorrhage. The results failed to show clinical improvement, and this early experience led to a general loss of enthusiasm for the use of fibrinolytic agents in acute stroke. In the 1970s, how-

ever, cardiologists clearly showed a clinical benefit with thrombolytic agents in patients with acute myocardial infarction.[15] In these patients thrombolytic agents have now become routine therapy, and urokinase, streptokinase, and tissue plasminogen activator (tPA) all provide effective coronary artery revascularization when administered in the first 6 to 12 hours. Lytic agents are associated with coronary reperfusion rates exceeding 80% when treatment is administered within hours.

With thrombolytic therapy, the goal is to establish reperfusion before tissue death. The demonstrated efficacy of thrombolytic therapy in acute myocardial infarction led to renewed interest in lytic therapy for stroke. A multicenter study with angiographically documented vascular occlusions and recanalizations showed a modest rate of reperfusion ranging from 20% to 40% using intravenous tPA. It appeared most successful in distal branch vessel occlusions.[16] Hemorrhagic infarction was common, although neurologic deterioration related to bleeding complications was not.

Alternative approaches in thrombolytic therapy appear necessary to improve effectiveness. Studies with intravenous tPA have attempted to shorten the interval to treatment in an effort to improve results.[17,18] Another technique has been to pursue the intra-arterial administration of the thrombolytic agent. The lytic agent can be delivered locally at the site of the occlusion or into the thrombus itself. This technique has achieved recanalization rates of 90% using streptokinase or urokinase.[19] Clinical improvement appeared associated with the establishment of reperfusion in preliminary series, and a randomized study of intra-arterial urokinase is underway.

Reperfusion Injury

Although reperfusion occurs as part of the natural history of embolic stroke and is the desired end point of one strategy in acute intervention, it may be associated with a cost of its own. Free radical-mediated injury has been proposed as a mechanism underlying reperfusion injury.[20] With ischemia the tissue develops a relative anaerobic metabolic state that returns to aerobic conditions with reperfusion. This sequence of events would favor oxidation and free-radical formation, although other mechanisms of free-radical formation are likely important as well. Toxicity was originally thought to arise from peroxidative damage to membrane lipids, but peroxidative damage has been shown to extend to proteins and DNA, which may play a more important role than lipid peroxidation.[21,22] Edema, both cytotoxic and vasogenic, has been shown to be induced by free-radical damage.

Confirmation of the validity of this concept comes from experimental stroke models. Transient ischemia followed by reperfusion was induced by unilateral carotid artery occlusion for three hours.[23] A 21-aminosteroid compound thought to scavenge oxygen-free radicals was given intravenously before carotid clamping and after reperfusion, leading to an increased amount of neuronal survival. Similar studies with other agents known to scavenge free radicals or inhibit formation have demonstrated similar neuronal sparing and decreased edema formation. A brisk inflammatory response accompanies reperfusion, and immune-mediated cellular damage likely also contributes to necrosis. Agents to blunt this immune response are also under laboratory study.

One of the 21-aminosteroid agents, tirilazad mesylate, is currently in clinical trial for ischemic stroke. Other agents that block free-radical tissue damage are becoming available for clinical trial.

Acute Stroke Intervention

Strategy	Mechanism of Action	Prototypic Agent	Effect
Neuronal protection	Block Ca^+ influx triggered by ischemia	Dextromethorphan	Minimize ischemic damage
Acute revascularization	Lyse occluding clot	Streptokinase	Restore circulation
Blood reperfusion imaging	Scavenge free radicals	Allopunnol	Minimize lipid, protein destruction

Figure 1.—Strategies are given for intervention in patients with acute stroke. Combining treatments may yield maximal benefit and improve neurologic outcome.

Innovations in Therapy

Over the past ten years innovative advances have been made in the understanding of cellular injury related to ischemia. Many of the therapeutic advances are driven by the profusion of pharmacologic data allowing logical intervention at multiple sites in the stroke process. Evolving stroke must be thought of in terms of the biochemical battles being fought in ischemic tissue and the interventions that must be launched to rescue tissue. Clearly no single strategy is likely to be uniformly successful in such a complicated problem. A rational intervention will ultimately include the administration of agents to provide protection against ischemia, reestablish perfusion, and limit reperfusion injury.

The clinical mandate now is to bring stroke care to a new level. There is every potential for therapy to be effective when administered in the first hours. This underscores the importance of community education and a reordering of old medical priorities. Patients need to report stroke symptoms to their physicians immediately, and the medical system must come to recognize stroke as a true neurologic emergency requiring urgent intervention. Much work remains to be done in terms of insightful clinical studies to select the most useful agents and to develop an efficacious treatment strategy.

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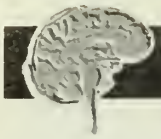

NEUROLOGY *Therapy*

Role of Steroids and Immunosuppression and Effects of Interferon Beta-1b in Multiple Sclerosis

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Multiple sclerosis (MS) is the most common cause of nontraumatic neurologic disability affecting young adults in the Northern Hemisphere. Although its cause remains unknown, recent technologic advances in immunology, molecular biology, and neuroimaging have improved our understanding of the pathogenesis of this disorder. Advances in symptom- and disease-modifying therapies have accompanied these improvements. In this article I review the effects that corticosteroids, immunosuppressants, and interferon beta-1b (IFN-β1b) have had in the management of MS. For each therapy a discussion of the possible mechanism of action is followed by a critical review of selected published clinical trials and a commentary on the effects of that experience on clinical practice and experimental therapeutics.

Glucocorticosteroids and Adrenocorticotropic Hormone (Corticotropin)

Glucocorticosteroids are the most commonly used treatment for the exacerbations of MS. Although the precise manner by which they exert their beneficial effect in MS remains unknown, possible mechanisms of action include a reduction of focal defects in the blood-brain barrier as shown by serial gadolinium-enhanced computed tomographic (CT) and T1-weighted magnetic resonance imaging (MRI) scans,[1-3] a reduction of edema associated with focal imaging abnormalities on T2-weighted MRI scans,[3] an improvement in axonal conduction,[4] a reduction in intrathecal immunoglobulin G synthesis and intensity of oligoclonal band staining,[5] and immunosuppression induced by the steroid-mediated blockade of cytokine gene expression.[6]

Glucocorticosteroids and Corticotropin for Acute Exacerbations of Multiple Sclerosis

The first clinical trials to suggest that glucocorticosteroids and corticotropin had clinical efficacy in the treatment of MS exacerbations were reported in 1951 and 1952.[7,8] These trials and other open uncontrolled trials of that era led to the sporadic use of these therapies in clinical practice. The subsequent publication of the "Cooperative Study in the Evaluation of Therapy in Multiple Sclerosis: ACTH vs Placebo"[9] further encouraged the use of corticotropin for MS exacerbations. Patients in this multicenter, double-masked study were randomly assigned to receive corticotropin gel, 40 units intramuscularly twice a day for seven days, 20 units intramuscularly twice a day for four days, and 20 units intramuscularly each day for three days, or matched placebo within eight weeks of an exacerbation. Considerably more patients treated with corticotropin (65%) than those receiving placebo (47%) had improvement in Kurtzke Disability Status Scale scores four weeks after therapy was initiated.[10] The duration of these benefits was not determined, as the patients were not observed for longer than four weeks. This study substantially influenced neurologic practice and established corticotropin as an accepted treatment of MS exacerbations.

The experience gained in planning and implementing the cooperative study also had a notable effect on the manner in which future clinical trials in MS would be conducted. This subsequent effect was due largely to the fact that several of the cooperative study investigators were also members of a panel convened in 1965 to evaluate experimental trials of therapy in MS. This panel published a list of problems associated with clinical trials in MS[11(p552)]:

> The difficulties inherent in judging the effects of therapy have been stressed. These are (1) lack of precision in the diagnosis; (2) the erratic and unpredictable course [of the disease]; (3) lack of a direct method for investigating activity of the disease; (4) the existence of only crude parameters for quantifying and recording the clinical course of the disease; (5) the irreversibility of gliosis and its masking effect on disease activity elsewhere in the nervous system; (6) psychological disturbances, including hysterical tendencies, in some patients; (7) problems of keeping large groups of patients under standard conditions of therapy or control for long periods (necessary because of the chronicity and erratic nature of the disease); (8) imprecise definitions of relapse.

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
IFN-β = interferon beta
IFN-β1b = interferon beta-1b
IV = intravenous
MRI = magnetic resonance imaging
MS = multiple sclerosis

This report also considered designs for comparing treatments, prestudy calculation of sample size, historical controls versus randomized parallel-treatment groups, the double-blind method of treatment assignment, the benefits and problems associated with matched-pair designs, inclusion and exclusion criteria, outcome variables, the difficulties in handling dropouts and incomplete follow-up, attention to the use of confidence intervals, and when there is no statistically significant difference, "the power of comparison." Many of the recommendations of this panel were incorporated into the design of the cooperative study. Thus, the design of this study became the gold standard for subsequent clinical trials in MS.

Corticotropin remained the preferred treatment of MS exacerbations until 1985. That year it was reported that patients treated with 1 gram of intravenous (IV) methylprednisolone for seven days were clinically more improved than patients treated with 60 units of intramuscular corticotropin tapered by 20 units each week for three weeks,[12] but the treatment benefit disappeared three months after therapy was initiated. Other investigators observed similar clinical improvements for 4 to 12 weeks with either a shorter course of IV methylprednisolone sodium succinate (1 gram daily for 3 days) or the corticotropin protocol used in the cooperative study (80 units for 7 days, 40 units for 4 days, and 20 units for 3 days).[13] Although clinical benefits appeared to be equal in these treatment groups, fewer adverse effects were observed with IV methylprednisolone. Similar benefits have resulted from alternative protocols of IV methylprednisolone administered in other double-blind, placebo-controlled, randomized clinical trials.[14,15] The doses used in these treatment protocols ranged from 15 mg per kg of body weight daily for 3 days tapered over 15 days, to 500 mg daily for 5 days. The administration of methylprednisolone, 500 mg per day IV for 5 days, has also been reported to reduce spasticity in patients with chronic progressive MS when compared with saline placebo.[15] This benefit was only evident for four weeks after therapy was initiated. These studies encouraged the clinical use of high-dose pulses of IV methylprednisolone for the treatment of MS exacerbations. Further support for this treatment was provided by the observation that high-dose IV methylprednisolone therapy reduced intrathecal immunoglobulin production,[1,16] plaque edema, and gadolinium enhancement evidenced by serial CT and MRI scans.[2,3] These effects were less evident with lower doses of corticosteroids.[2]

Although there is no agreement regarding the optimal dose or duration of IV methylprednisolone therapy for MS exacerbations, most neurologists currently administer between 500 and 1,000 mg of IV methylprednisolone daily for 3 to 7 days, followed by an oral prednisone taper from 60 mg for 10 to 21 days. This treatment can be administered safely on an outpatient basis unless neurologic or underlying medical conditions warrant admission to a hospital. This dose range of IV methylprednisolone is generally well tolerated, but insomnia, restlessness, euphoria, hypomania, and weight gain can be problematic.[17]

Corticosteroids and Corticotropin for Long-term Management of Multiple Sclerosis

Although steroids are widely used to manage acute attacks in patients with MS, their role in the long-term management of MS has not been rigorously investigated. It has been said that long-term daily use of corticosteroids does not substantially slow the progression of disability.[18] In 1961 the use of prednisolone (10 to 15 mg per day orally) was compared with that of aspirin (6 grams per day orally) and placebo in 86 patients observed for 18 months.[19] The trial was randomized, and patients were matched for disability, age, course, and disease duration. No difference was seen among treatment groups by measures of disability, exacerbation rate, or patient self-assessment at 6 or 18 months. In 1967 the results of the long-term treatment of MS with corticotropin were reported.[20] In this randomized, controlled, but unblinded study, 181 patients were treated with corticotropin (15 to 25 units intramuscularly daily; the dose was adjusted according to "facial mooning just evident") and compared with 169 patients who were treated with placebo. Patients were examined every 3 months for 16 months. No benefits were found in the corticotropin-treated group.

These limited data do not support the long-term use of corticotropin or oral prednisone. No studies have addressed the possible value of intermittent pulses of high-dose IV methylprednisolone as a disease-modifying therapy, but recent observations have led to increased enthusiasm for such a study. These include the following:

- Serial MRI studies have shown that new lesions are less likely to develop in patients with relapsing MS during the six-month period after a single course of IV methylprednisolone therapy than during the six-month period before initiating that therapy,[21] and
- Steroid treatment may delay the onset of MS in patients with isolated optic neuritis.[22]

A two-year study comparing the relative benefits of bimonthly pulses of 10 mg versus 500 mg of IV methylprednisolone to prevent disease progression is underway at the University of California, San Francisco-Mount Zion Multiple Sclerosis Center and the Cleveland Clinic (principal investigator, D.E.G.). A separate trial comparing IV methylprednisolone and IFN-β1b is being designed (principal investigator, R. W. Beck, MD). Because a double-blind design for comparing the use of IV methylprednisolone with that of IFN-β1b is thought to be impractical, it has been suggested that rigorously defined clinical end points determined by a single "blinded" ex-

amining physician may provide the most acceptable alternative design for this study.[23]

Use of Glucocorticosteroids and Corticotropin in the Treatment of Optic Neuritis

The first double-blind, placebo-controlled, prospective study of corticotropin use in optic neuritis was reported in 1966.[24] The authors found that the corticotropin-treated group recovered vision faster, but at one year the visual acuities of the two groups were not substantially different.[25] Similar results were reported for patients with optic neuritis treated with retrobulbar administration of triamcinolone.[26] There have been no double-blind controlled studies of oral prednisone therapy for this condition. Despite the lack of evidence of long-term benefits using these treatments, 59% of ophthalmologists and 81% of neurologists before 1992 were reported to use oral prednisone for the treatment of optic neuritis.[27]

This treatment practice was challenged by the results of the Optic Neuritis Treatment Trial reported in 1992.[28] In this study patients were randomly assigned to one of three treatment regimens: oral prednisone, 1 mg per kg daily for 14 days; IV methylprednisolone, 250 mg every six hours for 3 days, followed by oral prednisone, 1 mg per kg daily for 11 days; or oral placebo for 14 days. The first two regimens were followed by a short oral taper consisting of 20 mg on day 14 and 10 mg on days 16 and 18. This study was designed specifically to determine whether corticosteroids produce a benefit in visual function in either the short or the long term—that is, two years—in patients with acute idiopathic optic neuritis. In this regard the results of the study showed that compared with placebo, IV methylprednisolone accelerated the recovery of vision but did not improve visual outcome after one year, oral prednisone therapy did not improve visual outcome at any time, and more patients who received oral prednisone had subsequent optic neuritis than patients who received IV methylprednisolone. Although the effects of this trial on clinical practice have not yet been formally assessed, it is reasonable to predict that IV methylprednisolone therapy will replace the use of oral prednisone for the treatment of acute optic neuritis associated with impaired visual acuity.

Optic neuritis is frequently the first manifestation of MS.[29] For this reason the study group of the Optic Neuritis Treatment Trial has subsequently determined the proportion of patients in each treatment arm who during the 24-month trial period were diagnosed with clinically definite multiple sclerosis.[30] Patients receiving IV methylprednisolone had a reduced incidence of clinically definite MS during the two-year study period.[22] Although the study has some design limitations,[31] its results have the potential to change the routine clinical treatment of isolated acute optic neuritis. Should we extrapolate these observations to patients with isolated idiopathic acute myelopathy or isolated idiopathic brain-stem dysfunction? This seems premature, even though both of these conditions, particularly when associated with an abnormal MRI, have been shown to be associated with an increased risk of MS subsequently developing.[32,33] Further studies that examine the role of IV methylprednisolone therapy in patients with isolated optic neuritis, myelopathy, and brain-stem signs are needed.

Immunosuppressive Therapy

The use of immunosuppressant therapies in multiple sclerosis has been based on the hypothesis that it is an autoimmune disease. Although not proved, this hypothesis is supported by considerable empirical evidence derived from patients with MS and animal models of the disease, including the following:

- Similarities between MS and animal models of chronic relapsing experimental allergic encephalomyelitis,[34]
- Elevated intrathecal oligoclonal immunoglobulin production,[35]
- A characteristic distribution of cytokines and T-cell subsets within acute and chronic plaques of MS,[36]
- An association of disease frequency with specific HLA-DR haplotypes in several different ethnic groups and an MS susceptibility locus linked to the T-cell receptor β-chain complex,[37]
- Diminished suppressor cell number and function and possible correlation of these abnormalities with disease activity,[38]
- Clinical worsening seen with the administration of interferon gamma,[39] and
- Transient benefit seen with immunosuppressive therapy.[40]

Azathioprine

Azathioprine is a purine analogue designed as a "prodrug" to permit the slow liberation of the active metabolites 6-mercaptopurine and 6-thioinosinic acid into tissues. Because the maximal in vivo immunosuppressive effect requires three to six months of daily use, azathioprine is frequently combined with more rapidly acting corticosteroids. The precise mechanism of action is uncertain. Several studies have shown that it suppresses cell-mediated hypersensitivity reactions and produces alterations in antibody production.[41]

In all, 21 clinical trials of azathioprine use in multiple sclerosis have been published since the initial report in 1969 by Tucker and Kapphahn.[42] Seven of these trials were controlled and involved patients with either exacerbating or chronic progressive MS.[43-49] A meta-analysis of these seven studies demonstrates a small but significant benefit of azathioprine.[50] The relative odds of remaining exacerbation free for three years while taking azathioprine compared with placebo was 1.97.[50] This benefit compares favorably with the reduction in exacerbation rate reported with IFN-β1b in relapsing-remitting MS.[51] Similar to IFN-β1b, azathioprine offers only a modest degree of protection against the progression of disability. This effect is of questionable significance and requires two to three years before becoming evident.

Various manifestations of toxicity with azathioprine are common, but the cessation of therapy is necessary in less than 10% of patients with MS. Therapy is most commonly stopped because of drug-related fever, rash, or gastrointestinal intolerance.[52-54]

The slight but consistent reduction in relapse rate with limited toxicity and the availability of the drug have helped to establish azathioprine as the most commonly used immunosuppressant therapy in MS. In 1987 azathioprine was used as a standard treatment in some European MS treatment centers.[55,56] It is anticipated that its use will decline in this country as IFN-β1b becomes increasingly available. Considering its clinical risk-to-benefit profile and its favorable cost and ease of administration relative to IFN-β1b, azathioprine will probably continue to have a limited role in the management of patients with relapsing MS.

Cyclophosphamide

Cyclophosphamide is an alkylating agent with both cytotoxic and immunosuppressive effects. Monthly IV cyclophosphamide administration in doses ranging from 1,000 to 2,000 mg per m^2 of body surface results in a pronounced reduction of the number of T-helper or inducer cells and a less striking decrease in suppressor or cytotoxic cells in patients with MS.[57] Monthly pulses of IV cyclophosphamide for a year induced reductions in the numbers of suppressor or cytotoxic cells, natural killer cells, and in antibody-dependent cellular cytotoxicity functions lasting from one to two months. In addition, reduced B-cell numbers in these patients recovered in two to four months, whereas the recovery of helper cell subsets and total T-cell numbers, helper:suppressor ratio, and proliferative responses to mitogens took more than four months.[58] Others have found that the decrease in helper cell subset populations can still be demonstrated as long as 13.5 years after IV cyclophosphamide therapy (8 grams in 20 days).[59]

In 1983 the results of a randomized, unblinded trial comparing IV cyclophosphamide with corticotropin, corticotropin alone, and oral cyclophosphamide, corticotropin, and plasma exchange in 58 patients with chronic progressive MS were reported.[60] A statistically significant reduction in the proportion of patients experiencing clinical progression was seen after 12 months in the patients receiving cyclophosphamide with corticotropin. Of the cyclophosphamide-corticotropin-treated group, 80% were stabilized or had improved Kurtzke Disability Status Scale scores[10] at 12 months compared with 20% of the group receiving only corticotropin for 21 days. Although the benefits were no longer evident two years after therapy was initiated, this study offered a new treatment option for patients with chronic progressive multiple sclerosis. Neurologists began to use this drug shortly after this report appeared.

Other investigators began to explore the possibility that booster injections of cyclophosphamide might prolong the clinical benefits reported with cyclophosphamide induction. In one study, patients with chronic progressive MS were randomly assigned to bimonthly cyclophosphamide booster injections (700 mg per m^2) or no further cyclophosphamide treatment following completion of the Hauser induction regimen.[61] A trend was seen favoring the patients treated with booster injections, but this trend did not reach statistical significance. A subsequent report by the Northeast Cooperative Sclerosis Treatment Group suggested that bimonthly boosters were associated with prolonged stability of patients with chronic progressive MS.[62] Of the patients initially treated with induction and subsequently treated with bimonthly cyclophosphamide boosters, 38% were stable or improved compared with 24% of the patients who received only induction therapy. These findings encouraged the use of cyclophosphamide induction and subsequent bimonthly cyclophosphamide boosters by neurologists providing care to patients with multiple sclerosis.

In a placebo-controlled, single-blind study of IV cyclophosphamide therapy, 22 patients with MS received IV cyclophosphamide without corticosteroids or corticotropin, and 20 control patients received IV folic acid.[63] Twelve months after treatment, 64% of the cyclophosphamide- and 14 of the placebo-treated group (70%) showed evidence of stable or improved functional status as measured by disability status scale scores. The absence of any notable benefit found in this single-blind, placebo-controlled trial, as well as the toxicity that occurred in similarly treated patients in clinical practice, began to dampen initial enthusiasm for the use of cyclophosphamide in patients with chronic progressive MS. Support for this therapy eroded further after the report of the Canadian Cooperative Multiple Sclerosis Study Group Trial of plasmapheresis and cyclophosphamide in MS.[64] This multicentered, single-blind, randomized trial also failed to detect any important difference in treatment benefit in patients treated with IV cyclophosphamide and oral prednisone; daily oral cyclophosphamide, alternate-day prednisone, and weekly plasma exchange; and placebo medications and sham plasma exchange. The reasons for inconsistent results when using IV cyclophosphamide for patients with chronic progressive MS are not entirely clear but have been attributed to differences in drug doses, patient selection, and criteria for clinical deterioration.[65,66] The final report from the Northeast Cooperative Sclerosis Treatment Group suggests that benefits observed with cyclophosphamide treatment may be restricted to patients younger than 40 years and those with a secondary progressive as opposed to a primary progressive clinical course since disease onset.[64]

In summary, clinical benefits observed with cyclophosphamide therapy are generally marginal, and toxicity is frequently problematic. It may prove to be that benefits are restricted to MS patients who are younger than 40 with secondary progressive disease. At present most neurologists agree that cyclophosphamide has little benefit and substantial toxicity in patients older than 40 with a progressive course since their disease onset. A meta-analysis of the conflicting data from previous studies would be of considerable interest to clinicians who re-

main undecided whether to use cyclophosphamide as a possible treatment of patients with secondary chronic progressive MS who are younger than 40 years.

Interferon Beta-1b

In 1957 Isaacs and Lindenmann described a substance secreted by virus-exposed cells that "interfered with" viral replication and was accordingly called "interferon."[67] Since the original description, three molecular species of interferons—α, β, and γ—have been defined, initially by their antigenicity and subsequently by molecular cloning. All three species of interferons possess antiviral activity, but their other biologic activities show important differences.[41]

The rationale for using interferons as therapeutic agents in multiple sclerosis arises from their antiviral and immunomodulatory properties,[68] their limited toxicity with clinical use,[69] and the deficient production of both type I (IFN-α and IFN-β) and type II interferons (IFN-γ) by cells isolated from patients with multiple sclerosis.[70] Both recombinant (synthesized in the cell cultures programmed with interferon genes) and natural (purified from cell cultures stimulated to produce interferon) reagents have been administered. The greater purity and greater availability of the recombinant interferons have made them agents of choice for the applications.

The first trial of any interferon in the treatment of multiple sclerosis was reported in 1981.[71] In this randomized, controlled but unblinded pilot study, 20 patients were administered natural fibroblast IFN-β (1 million IU per m^2) by repeated lumbar punctures. The intrathecal route of administration was used because of concerns that IFN-β might not be able to cross the blood-brain barrier, as parenterally administered interferon could not be detected in the cerebrospinal fluid. These concerns were subsequently addressed by demonstrating that parenteral interferon regulates gene expression within the central nervous system.[72,73] Fewer exacerbations reportedly occurred in patients receiving IFN-β than in control patients.[71] Furthermore, exacerbation rates during the administration of IFN-β were lower than prestudy rates. Subsequently, a randomized double-blind trial of intrathecal IFN-β in multiple sclerosis showed a significant difference in exacerbation rates between treated and control patients.[74] Control patients in this study underwent sham lumbar punctures.

The first phase III trial of parenteral recombinant IFN-$\beta_{Ser\text{-}17}$ (IFN-β1b) has recently been completed.[51,75] In this 11-center study, 372 patients with exacerbating or remitting MS were randomly assigned to one of three treatment groups: placebo, 1.6 million IU of IFN-β1b, and 8 million IU of IFN-β1b, self-administered by subcutaneous injection every other day for two to three years. Patients selected for this study had at least two exacerbations during the two years before study entry. All patients were ambulatory without assistance and had a relatively recent diagnosis of multiple sclerosis (mean duration from diagnosis in the three groups ranged from 3.9 to 4.7 years). All groups were well matched for various demographic and disease characteristics. The primary end points of the study were the exacerbation rate and the proportion of patients remaining free from exacerbations.

The investigators found dosage-dependent therapeutic benefits for the active treatment groups as measured by the primary end points. Patients treated with 8 million IU of IFN-β1b had a 33% decrease in the on-study exacerbation rate compared with placebo recipients. Benefits were also seen for the severity of exacerbations, a secondary outcome measure. Of note is that all treatment groups continued to experience progression of impairment,[76] and no significant difference in the proportion of patients having sustained progression was observed among the three groups.

This was the first clinical trial of multiple sclerosis to show conclusively a difference in serial MRI activity favoring the active treatment groups compared with placebo recipients.[75] The placebo-treated group had a mean increase in lesion area of 17.1% after three years compared with a mean decrease of 6.2% in the high-dosage IFN-β1b group ($P = .002$). In addition, a separate subgroup of 52 patients from one study site underwent MRI every six weeks for two years. A 75% reduction in the rate of new lesion formation compared with placebo recipients was observed in patients who received high-dosage IFN-β1b. This finding played an important role in the release of IFN-β1b for relapsing MS because the reduction in exacerbation rate reported for this drug was no more impressive than that reported for azathioprine or copolymer.[48,77] Whether the reduction in MRI activity will eventually translate into a reduction of the progression of functional impairment remains to be seen. Clearly if such a benefit is found, it will take longer than three years to become evident.

The release of recombinant IFN-β1b (Betaseron) has already had a noticeable effect on neurologists, patients with MS and their families, and clinical investigators conducting ongoing clinical trials in MS. A new sense of therapeutic optimism is clearly evident. Although Betaseron has been released only for use for relapsing-remitting ambulatory MS, all patients with MS and their neurologists have shown a keen interest in obtaining this drug. Because the drug supply has been limited, a lottery was developed to ensure equal access for all eligible patients. Although well intentioned, the lottery has created a sense of panic in many patients who are fearful their condition will deteriorate while they are waiting for medication to become available. This sense of panic is often fueled by unrealistic therapeutic expectations. Neurologists have responded by providing educational materials to help patients understand the therapeutic potential of Betaseron. Many neurologists in an effort to minimize the panic experienced by their patients have also responded by quickly registering every MS patient for the lottery, whether ambulatory and relapsing, nonambulatory and relapsing, or with chronic progressive MS. As a result, some nonambulatory relapsing patients and ambulatory patients with chronic progressive MS have received low lottery numbers and an equal number of eligible ambula-

tory relapsing patients are possibly being denied early access to therapy. It is anticipated that this sense of urgency and the resulting inequities will resolve as the supply of Betaseron increases over the next two years.

Investigators have expressed concerns about the effect that Betaseron may have on the feasibility of undertaking new or completing ongoing clinical trials of alternative promising therapies for MS. It is expected that the release of Betaseron will result in increased patient attrition from ongoing clinical trials and decrease the patient pool available for enrollment in future studies. The ethical and practical considerations relevant to MS investigators conducting or planning future clinical trials have recently been reviewed.[78] It has been suggested that all clinical trial participants be notified of any newly approved therapy and given the opportunity to receive it. Future study feasibility may be improved by making use of survival analysis techniques that permit patients for whom treatment has failed who receive the promising new experimental drug or placebo to be removed from the study at the earliest possible time. This would free patients to receive the new approved therapy or alternative therapies.[78] It has also been suggested that clinical trial designs should provide for an external monitoring committee charged with the responsibility of stopping an ongoing study when inadequate enrollment or excessive patient attrition jeopardizes the study's feasibility.[78]

Summary

Corticosteroids, corticotropin, azathioprine, cyclophosphamide, and IFN-β1b have each had a substantial effect on the care of patients with multiple sclerosis and the design of subsequent clinical trials of experimental therapeutics for MS. The use of MRI scanning[76] and more sensitive clinical outcome measures[79] will possibly enable us to complete clinical trials in a fraction of the time required for earlier trials. The release of Betaseron, which favorably alters the attack rate in ambulatory patients with relapsing-remitting MS has brought a sense of renewed optimism to patients with MS, their families, and their care providers. New promising therapies for chronic progressive MS[80,81] and biologic products[82] possibly capable of enhancing the effects of IFN-β1b in patients with relapsing MS are setting the stage for additional important therapeutic advances in this disease.

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NEUROLOGY *Therapy*

Headache

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Headache-prone patients have many highly effective therapeutic options open to them. Used only at the time of headache, sumatriptan succinate by mouth or injection and dihydroergotamine nasal spray are novel choices now or soon to be available. The original migraine therapy, ergotamine, is highly effective in its rectal suppository formulation, when used at a subnauseating dosage. Valproate sodium is the latest addition to the many therapies available for long-term stabilization.

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Most of us are subject to headache from time to time. The mechanism for generating ordinary headaches may be activated by worry and anxiety, but stress does not appear to be necessary for the symptom to occur.[1,2] Genetic factors may augment this system, resulting in a susceptibility to more frequent or more severe head pain, with or without associated neurologic symptoms.[3] The term "migraine" is being used increasingly to refer to such a susceptibility to head pain in contradistinction to its previous usage as an aggregation of certain symptoms. Thus, stress-related headaches, perhaps the commonest syndrome reported by patients, are examples of the expression of this susceptibility after provocation by an adequate stimulus; a similar, if not identical, mechanism is identified by the activation of headache by red wine, normal menses, and exposure to glare and certain odors.[4]

The drugs that have proved to be effective in treating migraine were uncovered empirically or for actions later shown to be unrelated to the benefits observed clinically. These agents traditionally have been classified according to their actions in other conditions for which an effect outside the central nervous system has usually been implicated. Included in this group are vasoconstrictors (ergotamine tartrate, dihydroergotamine mesylate, sumatriptan succinate), serotonin antagonists (methysergide maleate, cyproheptadine hydrochloride), β-adrenergic receptor blockers (propranolol hydrochloride, nadolol), an antidepressant (amitriptyline hydrochloride), and antiprostaglandins (naproxen, ketoprofen) (Figure 1). There is evidence that the effect of propranolol in migraine is mediated by an action other than, or in addition to, β-adrenergic receptor blockade and, similarly, that amitriptyline probably does not act as an antidepressant. Although it is possible that some of these actions are relevant to the drugs' effectiveness in migraine, several lines of evidence suggest that their common mode of action may be to stabilize central inhibitory mechanisms.[5]

The introduction of sumatriptan, a selective agonist of a specific subgroup of serotonin receptors and an unusually effective agent in aborting acute headache attacks, has awakened interest in the treatment of this common ailment. In this review I focus on therapeutic advances in this area.

Treatment of Acute Headache or Migraine

In general, an adequate dose of whichever agent is chosen should be used at the start of an attack. If additional medication is required in 30 to 60 minutes because symptoms return or have not abated, the initial dosage should be increased for subsequent attacks. Drug absorption is impaired during attacks because of reduced gastrointestinal motility. Absorption is delayed in the absence of nausea and is related to the severity of the attack but not the duration.[6] Therefore, when oral agents fail, the major options are rectal administration of ergotamine, subcutaneous sumatriptan, parenteral dihydroergotamine, and intravenous chlorpromazine hydrochloride or prochlorperazine maleate.

For patients with a prolonged buildup of headache, oral agents may suffice. When aspirin and acetaminophen fail, the addition of butalbital and caffeine to these analgesics is highly effective; ibuprofen (600 to 800 mg) and naproxen (375 to 750 mg) are often useful. Isometheptene compound,* one to two capsules, is effective for mild to moderate "stress headaches."[7] When these measures fail, more aggressive therapy should be considered.

Ergotamine Tartrate

The oral and rectal absorption of ergotamine tartrate is unpredictable, as it varies widely among individual patients. Bioavailability is less than 5% for the oral dosage form, but it is considerably higher after rectal dosing.[8] Peak plasma concentrations are reached about an hour after oral or rectal dosing. Plasma levels after rectal admin-

*All isometheptene compounds contain 65 mg of isometheptene mucate, 100 mg of dichloralphenazone, and 325 mg of acetaminophen.

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ABBREVIATIONS USED IN TEXT

DHE = dihydroergotamine
NSAIDs = nonsteroidal anti-inflammatory drugs

istration are higher; one study showed levels 20 times higher.[9] Effectiveness, as assessed by peripheral arterial constriction, is much greater after rectal than oral administration of the drug. Its biologic effects last much longer than its short elimination half-life of two to three hours would suggest.

Ergotamine produces powerful and selective constriction of the external carotid artery and its branches. Only slight α-adrenergic blockade occurs at doses used clinically, and the vasoconstrictor effect is mediated by a direct effect on arterial serotonin receptors. Extracranial arterial constriction is likely important to ergotamine's efficacy, but the extracranial arteries may not be the drug's primary site of action. Several ergot alkaloids have been found to depress the firing rate of serotonergic neurons of the brain-stem raphe, the origin of inhibitory projections to the forebrain; thus, stabilization of this system may be the major mode of action of ergotamine.[5]

An adequate dose should be taken as soon as possible—not divided into half-hourly or hourly supplements; if the initial dose fails, subsequent doses usually fail also. If possible, a dose that does not cause nausea should be determined. A dose that provokes nausea—probably a centrally mediated side effect—is too high and may even intensify a migraine attack. The appropriate dosage of ergotamine is best arrived at by determining the patient's capacity to tolerate ergotamine during a headache-free period. The average dose of a rectal suppository is half (1 mg), so that if a patient is seen for the first time during a headache attack, I give 1 mg immediately, and if there is no evidence of improvement in 45 minutes, another 1-mg dose may be given.

Dihydroergotamine Mesylate

Introduced about ten years after ergotamine, dihydroergotamine mesylate (DHE) was found to be at least equally effective in aborting acute attacks of migraine. In contrast to ergotamine, DHE produces only modest arterial constriction[10] but is a potent venoconstrictor.[11] As with ergotamine, idiosyncratic hypersensitivity to the drug occasionally occurs, and rare instances of severe peripheral arterial spasm and coronary spasm have been reported.[12] Unlike ergotamine, DHE does not produce physical dependence.[13]

Given intravenously, DHE produces less nausea than ergotamine, and thus, if preceded by an antiemetic, it can be used when a migraine attack is attended by vomiting.[14,15] Subcutaneous or intramuscular administration of 1 mg usually suffices for 90% of patients.[16] Patients can be taught to administer a subcutaneous dose. A nasal instillation form is not as effective.

Adverse effects of the drug may include diarrhea, leg muscle pain, and abdominal discomfort. Patients with Prinzmetal's angina should be excluded from this therapy

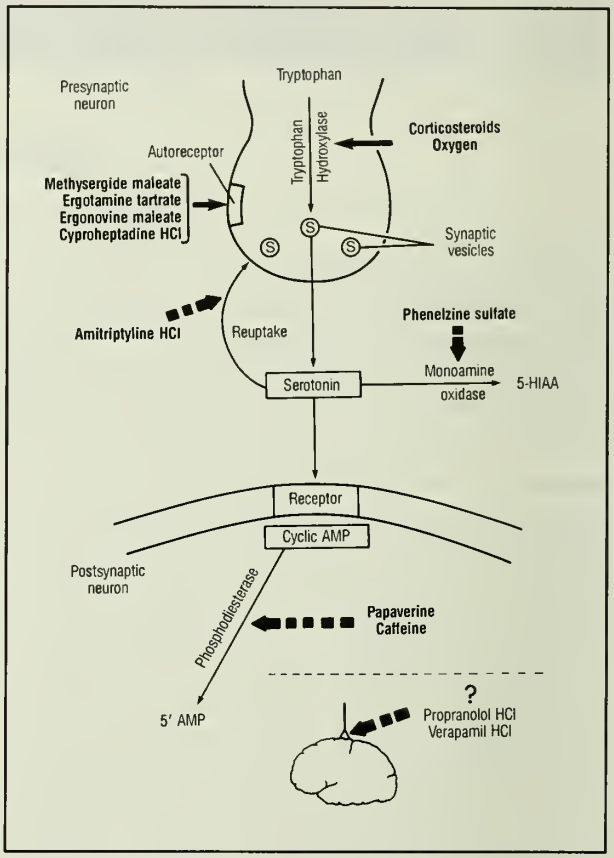

Figure 1.—The diagram shows the actions of the antimigraine drugs at the brain-stem and forebrain synapses. The **solid arrows** indicate stimulative or agonist properties; the **segmented arrows** indicate inhibitory properties. 5′ AMP = 5′-adenosine monophosphate, cyclic AMP = adenosine 3′:5′-cyclic phosphate, HCl = hydrochloride, 5-HIAA = 5-hydroxyindoleacetic acid

because of the risk of precipitating attacks through ergot hypersensitivity. Like other ergot derivatives, DHE is contraindicated in pregnancy.

The venoconstrictor effect of DHE persists for about eight hours after intravenous administration.[11] The major metabolite of DHE, 8′-hydroxy-dihydroergotamine, reaches plasma concentrations that are five to seven times higher than those of DHE itself and possesses similar pharmacologic effects.[17] Pharmacodynamic efficacy persists after drug withdrawal and in the absence of measurable drug levels.[11] Both DHE and its major metabolite bind selectively to brain serotonin receptors. Dihydroergotamine's lack of important arterial constrictor effects emphasizes the importance of these central receptor actions to the agent's action in migraine.

Phenothiazines

Two controlled studies have clearly demonstrated that intravenous chlorpromazine hydrochloride, 0.1 mg per kg of body weight,[18] and prochlorperazine maleate, 10 mg,[19] are highly effective in terminating migrainous episodes. The chlorpromazine protocol allowed for repeating the dose every 15 minutes as needed for a total of three doses; of the 24 patients who received chlorpromazine, 6 re-

TABLE 1.—*Drug Stabilization of Migraine*

Drug	*Tablet Size, mg*	*Daily Dose Range, mg*	*Most Common Side Effects*
Propranolol hydrochloride	10, 20, 40, 60, 80, 90 Sustained-release: 60, 80, 120, 160	40-320	Fatigue, insomnia, lightheadedness, impotence
Amitriptyline hydrochloride	10, 25, 50, 75, 100	10-175	Sedation, dry mouth, appetite stimulation
Ergonovine maleate	0.2	0.4-2.0	Nausea, abdominal pain, leg tiredness, diarrhea
Verapamil hydrochloride	40, 80, 120 Sustained-release: 120, 180, 240	160-480 320-960	Constipation, nausea, fluid retention, lightheadedness, hypotension
Valproate sodium	125, 250, 500	375-2,500	Nausea, tremor, alopecia, appetite stimulation
Phenelzine sulfate	15	30-90	Sedation, orthostatic hypotension, constipation, urinary retention
Methysergide maleate	2	2-12	Nausea, abdominal pain, insomnia, appetite stimulation, fluid retention, limb claudication

quired only one dose, 9 received two doses, and another 9 had three doses. Because phenothiazines confer no physical dependence, these results have important practical implications. Prochlorperazine and DHE are miscible, so that both drugs may be administered simultaneously with a single venipuncture.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have become important for the treatment of migraine,[20,21] in part because they do not generate a cycle of dependency. The NSAIDs are analgesic when tested in acute pain models, and this property can be shown to be independent of prostaglandin synthesis inhibition,[22,23] which is the common pharmacologic action of drugs in this class. Evidence is emerging that the central actions of NSAIDs best explain their analgesic properties. The analgesic actions of acetylsalicylic acid and acetaminophen may also be centrally mediated.[24-26]

Among the NSAIDs, naproxen is favored for migraine treatment because of its efficacy, tolerance, and safety record. It is completely absorbed after oral or rectal administration, with peak plasma concentrations reached an hour after naproxen sodium administration and two hours after naproxen administration.[27] The more rapid absorption of the sodium salt enhances efficacy for the management of acute headache episodes. The biologic half-life of naproxen is 12 to 15 hours. Plasma levels increase linearly with doses as high as 750 mg; at higher doses they continue to rise, although at a lesser rate. Thus, for an acute attack, a dose of no less than 750 mg should be considered.

Initial enthusiasm for this group of drugs for daily use must now be tempered because of the enteropathy that occurs with long-term use. When used for six months or longer, subclinical intestinal inflammation and occult blood loss develop in more than two thirds of patients.[28] As many as a fifth of them have bile acid malabsorption, and thus diarrheal illnesses may develop. Fewer than 1% have ulceration and strictures. In view of this experience and because there are so many alternatives for prophylaxis, the NSAIDs should not be used long term and daily in migraine therapy.

Sumatriptan Succinate

Sumatriptan was developed as an agonist specific to serotonin receptors, which occur not only in the midbrain dorsal raphe but also in the extracranial vasculature. Unique among antimigraine drugs, sumatriptan is devoid of activity in receptor systems other than serotonin receptors, probably accounting for its mild side-effect profile. The selective action of sumatriptan provides an important clue to the effective mode of action of other antimigraine drugs that have multiple sites of activity because sumatriptan binds only to serotonin receptors and effectively terminates migraine symptoms.[29]

Sumatriptan is distinctive in being the most extensively studied antimigraine agent in history; moreover, the studies have been rigorously controlled so that the efficacy of this drug is clearly established. Sumatriptan succinate reduces the intensity of acute headache attacks from "moderate to severe" to "mild or none" within two hours in 50% to 70% of patients following the oral administration of 100 mg and within an hour in 70% to 80% of patients following subcutaneous doses of 6 mg.[30] Headache recurs in 40% of patients within 24 hours, requiring another dose of the drug, probably because of its short half-life (2 hours).

Sumatriptan is effective for headache episodes that already peaked at the time of dosing, such as the early morning headache syndrome[32] and in menstrual-associated headaches,[33] the latter commonly waking women from sleep. Many patients say that they feel normal 15 minutes after taking a subcutaneous dose. No good data comparing sumatriptan with DHE are available; sumatriptan costs over four times more than DHE does.

The side-effect profile of sumatriptan is remarkably mild: warmth and tingling of the head and trunk are common and resolve shortly. Moreover, nearly 5% of patients report some chest discomfort that only rarely has been caused by myocardial ischemia. There is a consistent constrictor effect on the coronary artery circulation,[34] so that patients with coronary artery disease ought not receive this drug. For those at risk for coronary artery disease, such as older patients or those with diabetes mellitus or hypercholesterolemia, it has been suggested that the first dose of the drug be given with medical supervision.[35] It

also follows that sumatriptan and ergotamine should not be used concurrently.

Migraine Stabilization

A substantial number of drugs that have the capacity to stabilize the mechanism generating the symptoms that physicians recognize as migraine are now available. The probability of success with these drugs is greatly reduced in a patient with a drug-dependence cycle.[36] Such dependence can occur with ergotamine,[37] benzodiazepines,[36] corticosteroids,[39] all opiate analgesics, and aspirin and acetaminophen.[39] Any patient using analgesics daily without an interruption of 48 hours or more may be dependent and, therefore, not likely to benefit from antimigraine therapy until withdrawal is carried out. Intravenous DHE or phenothiazine therapy given in a hospital may be necessary for patients who sustain severe "rebound" headaches when they attempt withdrawal by simple abstinence.

If dependence is not a problem, the probability of success with any one of the antimigraine drugs is 60% to 70%, so that if one drug regimen is assessed each month, there may be an interval of several months before a patient's condition becomes stable. During this period it is usually necessary to provide the patient with an effective method for dealing with headache attacks that will not cause dependence; DHE and naproxen are highly suited for this purpose. Most patients are successfully managed with sequential monthly use of ergonovine maleate, propranolol hydrochloride or nadolol, and amitriptyline hydrochloride or nortriptyline hydrochloride (Table 1). If the situation demands urgent resolution, treatment with methysergide maleate or phenelzine sulfate can be implemented. The calcium channel antagonists have been disappointing.[40,41] Based on reports[42,43] and personal experience, valproate sodium appears to be remarkably effective.

Once effective stabilization is achieved, the drug therapy is continued for five to six months and then the dosage slowly tapered to assess its continued need. Many patients are able to discontinue medication and have fewer and less severe attacks for long periods of time,[44,45] suggesting that these drugs may alter the natural history of migraine.

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NEUROLOGY *Therapy*

Treatment of Parkinson's Disease

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Pharmacotherapy with levodopa for Parkinson's disease provides symptomatic benefit, but fluctuations in (or loss of) response may eventually occur. Dopamine agonists are also helpful and, when taken with low doses of levodopa, often provide sustained benefit with fewer side effects; novel agonists and new methods for their administration are therefore under study. Other therapeutic strategies are being explored, including the use of type B monoamine oxidase inhibitors to reduce the metabolic breakdown of dopamine, catechol-O-methyltransferase inhibitors to retard the breakdown of levodopa, norepinephrine precursors to compensate for deficiency of this neurotransmitter, glutamate antagonists to counteract the effects of the subthalamic nucleus, and various neurotrophic factors to influence dopaminergic nigrostriatal cells. Surgical procedures involving pallidotomy are sometimes helpful. Those involving cerebral transplantation of adrenal medullary or fetal mesencephalic tissue have yielded mixed results; benefits may relate to the presence of growth factors in the transplanted tissue. The transplantation of genetically engineered cell lines will probably become the optimal transplantation procedure.

The cause of Parkinson's disease may relate to oxidant stress and the generation of free radicals. It is not clear whether treatment with selegiline hydrochloride (a type B monoamine oxidase inhibitor) delays the progression of Parkinson's disease, because the drug also exerts a mild symptomatic effect. Daily treatment with vitamin E (a scavenger of free radicals) does not influence disease progression, perhaps because of limited penetration into the brain.

(Aminoff MJ: Treatment of Parkinson's disease, *In* Neurology—From Basics to Bedside [Special Issue]. West J Med 1994; 161:303-308)

Parkinson's disease is an idiopathic, chronic neurologic disorder characterized by some combination of tremor, rigidity, bradykinesia, and postural instability. It is generally progressive and leads to increasing disability with time. The disorder results from a disturbance of function of the basal ganglia that is due, in turn, to a loss of dopaminergic cells in the substantia nigra, a pigmented region of the midbrain.

Major advances have occurred during recent years in the treatment of Parkinson's disease, based in part on fresh insights into its pathophysiology gained from the development of animal models of parkinsonism. Parkinsonism may be induced in humans and nonhuman primates—and in certain other animals—by exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a protoxin that is converted to *N*-methyl-4-phenylpyridinium (MPP^+), the active toxin, by monoamine oxidase B. The toxin is taken up selectively by dopaminergic neurons in the substantia nigra through an active transport system that is normally responsible for dopamine reuptake,[1,2] and MPP^+ then inhibits oxidative phosphorylation, probably by a specific inhibition of mitochondrial complex I in the respiratory chain.[3,4] This leads to the destruction of nigrostriatal neurons, to dopamine depletion in the basal ganglia, and thereby to parkinsonism. The neuronal death probably results from the generation of free radicals by the interaction of MPP^+ with complex I.[4] The MPTP model provides a useful framework for understanding the naturally occurring disease in humans, suggesting pathogenetic mechanisms and therapeutic approaches that can be tested experimentally.

This review is directed at therapy for Parkinson's disease and considers both symptomatic treatment and measures to influence the rate of disease progression. Attention is given not only to current therapeutic approaches but also to novel strategies that are being developed or tested. Contrary to popular belief, the treatment of neurologic disorders in general and of Parkinson's disease in particular is substantive, the response to treatment is often gratifying, and the recent development of new therapies has been based on rational scientific principles.

Symptomatic Pharmacologic Treatment

For many years, the only symptomatic therapy for Parkinson's disease was with nonselective muscarinic antagonists (anticholinergic drugs) that had been found empirically to help in some cases. These agents are of limited clinical use, however, and are often poorly toler-

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ABBREVIATIONS USED IN TEXT

COMT = catechol-*O*-methyltransferase
MPP^+ = *N*-methyl-4-phenylpyridinium
MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
PHNO = 4-propyl-9-hydroxynaphthoxazine

ated, especially by older patients. The introduction in the 1960s of amantadine—an antiviral agent that was found by chance to have some antiparkinsonian action—led to disappointment when the drug failed to live up to initial expectations: many patients did not respond to it or had only short-lived benefit.

Subsequent therapeutic approaches have had a more scientific basis. One of the characteristic pathologic features of Parkinson's disease is degeneration of the substantia nigra (Figure 1), although other regions, such as the locus ceruleus, are also affected. A loss of dopaminergic neurons in the substantia nigra, with a resulting depletion in the striatal dopamine concentration, was recognized about 30 years ago to underlie many of the motor abnormalities of parkinsonism. This led to replacement therapy with levodopa (Figure 2), the metabolic precursor of dopamine, with resulting symptomatic benefit in most patients with true Parkinson's disease. As experience with levodopa accumulated, however, controversy developed about the optimal time of initiating levodopa therapy, based on concerns that levodopa may lose its effect with time or even exert a deleterious effect on the course of the disease. A recent study found that the timing of the introduction of levodopa influenced neither disease progression nor response to treatment, suggesting that treatment with this agent should be initiated in response to a patient's clinical state rather than delayed because of concern about possible long-term side effects.[5] The dose of levodopa should be kept to a minimum, however, to reduce the risk for the development of late side effects.

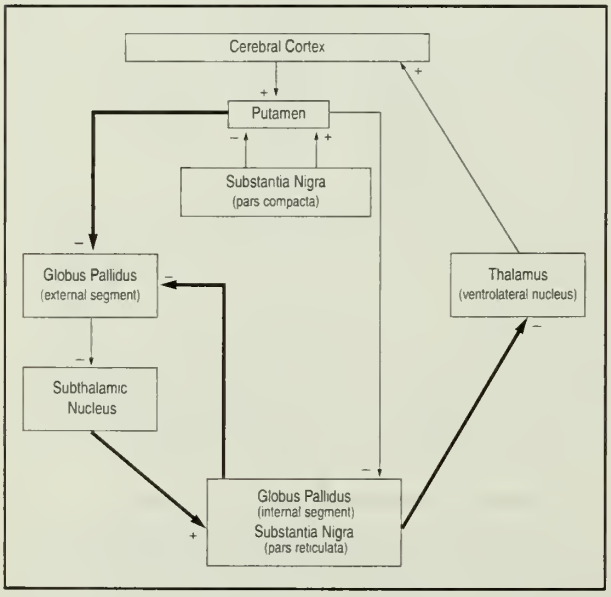

Figure 1.—Functional circuits are shown between selected cerebral structures involved in motor control. Excitatory circuits are indicated by + and inhibitory circuits by –. With the degeneration of the pars compacta of the substantia nigra that occurs in Parkinson's disease, there is increased activity in the projection pathways, indicated in the figure by bold lines.

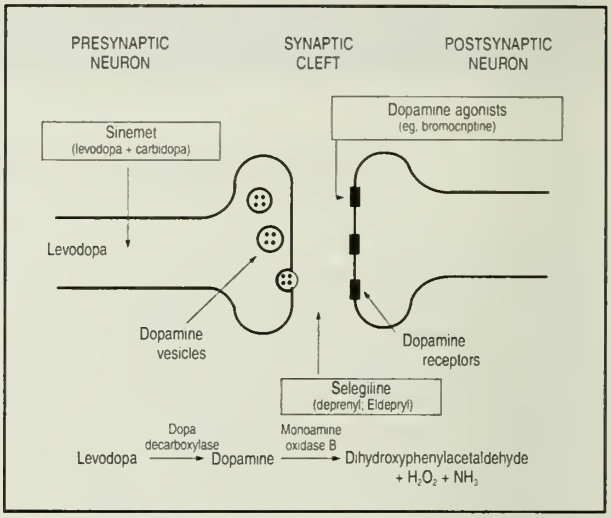

Figure 2.—The diagrammatic representation of dopaminergic therapy for Parkinson's disease shows the site of action of different therapeutic agents (given in boxes).

A major barrier to the absorption of levodopa is the presence in the intestinal mucosa of dopa decarboxylase, which converts levodopa to dopamine; in consequence, the greater part of an ingested dose of levodopa fails even to reach the general circulation.[6] Administering an extracerebral dopa-decarboxylase inhibitor with levodopa reduces both this extracerebral breakdown and any side effects of levodopa resulting from its peripheral actions. Levodopa is therefore administered routinely in combination with a peripheral dopa-decarboxylase inhibitor (carbidopa or benserazide) to increase the amount of levodopa reaching the brain; in the United States the combination of levodopa and carbidopa is available commercially as Sinemet (DuPont Merck). Certain side effects, such as nausea and vomiting, are less common with the use of Sinemet than with levodopa taken alone. After a few years of treatment, however, many patients who initially responded well to levodopa begin to have adverse reactions characterized by a wearing-off effect or by response fluctuations that seemingly have no relation to the timing of medication ("on-off" phenomenon). These complications can be disabling and pose major management problems. The duration and severity of disease and the duration of levodopa therapy have been implicated in their cause; proposed pathophysiologic mechanisms include the pharmacokinetics of levodopa, the degeneration of presynaptic dopaminergic nerve terminals, altered sensitivity of dopamine receptors, and abnormalities of nondopaminergic neurotransmitter systems.

Gastric emptying, which is erratic, markedly affects the absorption of levodopa. Such erratic absorption may account in part for any fluctuations in clinical response that occur during the day.[7] Levodopa is absorbed from the small intestine and transported across the blood-brain bar-

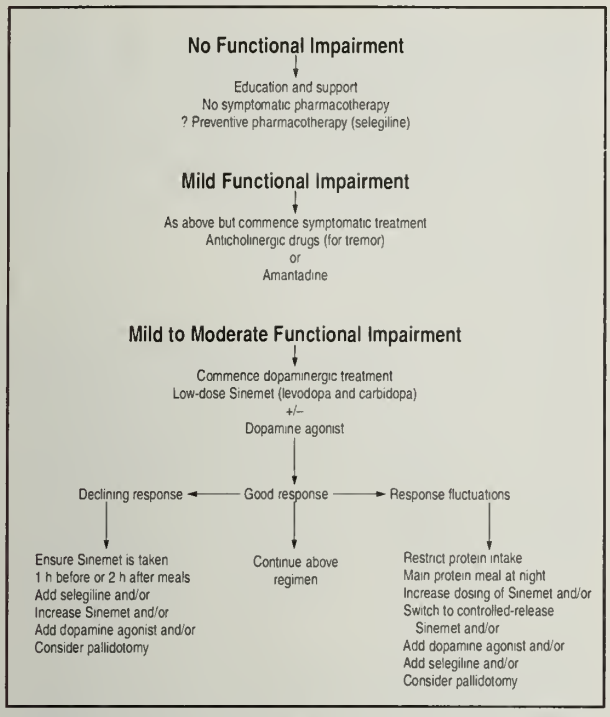

Figure 3.—The selection of treatment of Parkinson's disease is shown in this flow chart.

rier by an active carrier system that is also involved with the transport of certain other amino acids. Large protein meals reduce both the absorption of levodopa and its transport from the blood into the brain. In patients with the on-off phenomenon, then, restricting dietary protein intake to the minimum daily recommended allowance and scheduling the main protein intake to the last meal of the day are important management strategies to reduce response fluctuations (Figure 3). Fluctuations in response to oral levodopa can be overcome by continuous dopaminergic stimulation and are therefore reduced by a continuous infusion of levodopa intravenously, into the duodenum or, to a lesser extent, into the stomach.[8-10] A controlled-release formulation of Sinemet is now available and is sometimes helpful in reducing dosing frequency and maintaining steady blood concentrations of levodopa. It had been hoped that this would reduce the incidence of response fluctuations, but in many patients any benefit in this regard has been disappointing.

Abnormal involuntary movements may result from levodopa therapy, probably because of supersensitivity of postsynaptic dopamine receptors. Such dyskinesias may be present constantly, at times when plasma levodopa levels reach a peak, or at certain levels of plasma levodopa (and not at concentrations above or below this point). Correct management depends on determining the temporal pattern of the dyskinesia. When dyskinesias occur only at a certain submaximal blood concentration of levodopa, maintaining the concentration above this point by adjusting the dose may eliminate or greatly reduce them; by contrast, when dyskinesias coincide with peak blood concentrations of levodopa, a reduction in dose may be helpful.

Dopamine agonist drugs may alleviate symptoms by directly stimulating central dopamine receptors. Unlike levodopa, they do not require enzymatic conversion to an active metabolite, and their absorption and subsequent distribution to the brain are less erratic. The agents currently used in the United States are bromocriptine mesylate and pergolide mesylate; lisuride is in widespread use elsewhere, but is not approved by the Food and Drug Administration. Studies with bromocriptine, in particular, have shown that its early introduction in association with low-dose Sinemet therapy not only leads to sustained benefit but reduces the incidence of later complications such as response fluctuations and dyskinesias.[11,12]

New Approaches to Symptomatic Treatment

Recent work on the symptomatic treatment of Parkinson's disease has focused on the development of new dopamine receptor agonist drugs and of novel methods of administering them. Drugs to inhibit the breakdown of dopamine in the brain and of levodopa in the periphery are also being developed, as are various other pharmacologic strategies.

Dopaminergic Agents

Several new dopamine agonists are currently undergoing clinical trials. Some are more selective D-2 agonists and may therefore provide greater antiparkinsonian benefit with fewer side effects than the agonists currently in use.

New means of administering dopamine agonists may result in a steadier clinical response. Continuous dopaminergic stimulation by the subcutaneous administration of lisuride (a water-soluble D-2 receptor agonist) by a portable mini-infusion pump reduces fluctuations in response to oral levodopa,[13] but psychiatric complications have limited the long-term use of this approach.[14] The subcutaneous administration of apomorphine hydrochloride (a D-1 and D-2 agonist) similarly diminishes the incidence of response fluctuations,[15,16] in some patients for more than two years.[15] Administering dopamine agonists transdermally may also be helpful. For example, the transdermal administration of the D-2 agonist, 4-propyl-9-hydroxynaphthoxazine (PHNO), in conjunction with oral levodopa, leads to a more sustained response and less fluctuation than with levodopa taken alone,[17] but PHNO itself has had to be withdrawn for toxicologic reasons. In rats, the delivery of levodopa by subcutaneous implantation of a slow-release polymer matrix system leads to constant plasma concentrations of the drug for several months.[18] Such an approach may be helpful in humans in the future.

Monoamine Oxidase Inhibitors

Another novel approach to the symptomatic treatment of Parkinson's disease is by inhibiting the oxidative breakdown of dopamine by type B monoamine oxidase. Selegiline hydrochloride (deprenyl; Eldepryl, Somerset) inhibits this enzyme. It has therefore been used for some

years in Europe to augment the effect of dopamine by retarding its breakdown and thereby to treat patients in whom administered levodopa is either losing its effect or leading to response fluctuations. Such benefits are often minimal or transient, however, and selegiline is therefore usually prescribed for other purposes (discussed later under Preventive Treatment).

Catechol-O-Methyltransferase Inhibitors

The inhibition of dopa decarboxylase (by the carbidopa component of Sinemet) leads to a compensatory action of other pathways for the metabolism of levodopa, especially catechol-*O*-methyltransferase (COMT), and this leads to increased circulating levels of 3-*O*-methyldopa. The 3-*O*-methyldopa competes with levodopa for an active carrier mechanism involved in its transport across the intestinal mucosa and the blood-brain barrier. Selective COMT inhibitors may therefore enhance the benefits of levodopa therapy by reducing the conversion of levodopa to 3-*O*-methyldopa and increasing the availability of levodopa in the brain itself. Clinical studies are currently in progress to evaluate their therapeutic role.

Other Neurotransmitters

Other peptides and neurotransmitters present in the basal ganglia may also be affected in Parkinson's disease. For example, noradrenergic neurons of the locus ceruleus are known to be involved. The norepinephrine precursor, DL-threo-dihydroxyphenylserine has been given to certain parkinsonian patients with "freezing" or pronounced immobility that was unresponsive to dopaminergic therapy. Benefit was reported by some authors[19,20] but not others.[21]

There is evidence accumulating that increased activity of the subthalamic nucleus is important in producing parkinsonian deficits. This nucleus receives a glutamatergic input from the cortex and gives off glutamatergic efferent fibers to the substantia nigra and globus pallidus. Certain antiparkinsonian agents with known anticholinergic or antihistaminic properties are now recognized to be glutamate antagonists.[22] Other glutamate antagonists may therefore benefit patients with Parkinson's disease.[22] Experimentally induced parkinsonism is lessened by blocking excitatory amino acid transmission in the medial globus pallidus.[23] In rats and monkeys with pharmacologically induced parkinsonism, antagonists of certain glutamate receptors have antiparkinsonian effects and potentiate the effects of levodopa.[24] Therapeutic strategies based on glutamate antagonists may thus be rewarding, but await appropriate trials.

Neurotrophic or Growth Factors

Another new approach to the treatment of Parkinson's disease is with neurotrophic factors. A possible role in this regard for GM_1 ganglioside has recently been suggested.[25] Primates with MPTP-induced parkinsonism show a partial restoration of striatal dopamine levels following treatment with GM_1 ganglioside.[25] Whether this effect is mediated by the trophic support of degenerating dopaminergic cells or through the stimulation of fiber growth in the striatum is not clear. Again, muscle-derived differentiation factor (MDF) increases dopamine synthesis in damaged (but not intact) nigrostriatal dopaminergic cells.[26] Brain-derived neurotrophic factor (BDNF) is of especial interest because it protects dopaminergic neurons from the toxic effects of MPP^+ and 6-hydroxydopamine.[27,28] Other neurotrophic factors may also influence dopaminergic nigrostriatal cells.[27]

Surgical and Transplantation Procedures

Destructive surgical procedures have been in use for the treatment of parkinsonism for 40 years, but fell into disfavor with the introduction of levodopa. There has been a recent resurgence of interest in such procedures, however, for patients responding poorly to pharmacologic maneuvers. In particular, posteroventral pallidotomy may be especially effective in relieving tremor, rigidity, and bradykinesia in such circumstances.[29] The procedure is best reserved for patients with advanced disease that has become unresponsive to medical treatment or patients with intolerable side effects of medication.

A novel surgical approach involves cerebral transplantation procedures. In a pharmacologically induced rodent model of Parkinson's disease, grafting of adrenal medullary tissue—which is rich in dopamine—into the lateral ventricles and striatum leads to a reduction in abnormal motor activity.[30] The mechanism involved is unclear; the grafted tissue may act as a source of catecholamines and other neurotransmitters or of some neurotrophic factor. Sprouting of endogenous nerve terminals in the striatum has been observed after the transplantation of adrenal medullary tissue in animals, regardless of the survival of the grafted tissue,[31,32] and the importance of nerve growth factor has been illustrated more directly.[33]

Grafting adrenal medullary tissue into nonhuman primates also leads to a reduction of parkinsonian deficits. In humans with Parkinson's disease, however, the results of grafting portions of the patients' adrenal medulla (autografts) into the caudate nucleus have generally been disappointing despite dramatic early reports of benefit.[34-36] Nevertheless, some studies have yielded encouraging data that medication could be reduced, "on" time increased, or quality of life improved by the procedure, at least temporarily.[37,38] In fact, the grafted tissue often fails to survive.[39] The reason for the disparate results is unknown. It has been suggested that the addition of nerve growth factor to the transplanted tissue may improve the clinical response, but this awaits adequate demonstration. In experimental studies in monkeys, however, grafted adrenal medullary tissue has been shown to survive longer if myelinated peripheral nerve tissue (a source of nerve growth factor) is transplanted into the striatum with it.[40,41]

The use of transplantation procedures involving mesencephalic fetal tissue is another therapeutic approach that is under investigation.[42] Pronounced improvement has been reported in two American patients with MPTP-induced parkinsonism,[43] and more moderate benefit has followed such procedures performed in the United States in

patients with typical Parkinson's disease.[44,45] The experience in other countries has been summarized elsewhere by Ahlskog,[46] who emphasized the difficulty in comparing outcomes in different series because of the heterogeneity of patients, the varied rating procedures, and differences in follow-up. In no case was there complete reversal of parkinsonian symptoms, although in some patients disability was reduced. Most patients received unilateral grafts, but clinical improvement was often bilateral, with benefit typically beginning several weeks after transplantation. There have been concerns about ethical aspects of this approach and the limited amount of fetal tissue available for use. Many other issues remain to be resolved, including the optimal amount of graft tissue and the site of its deposition, the necessity for immunosuppressant therapy, and the need for growth factors.

The most effective surgical procedure for treating Parkinson's disease may ultimately involve the transplantation of genetically engineered cell lines, and work along these lines is already proceeding.[47]

Preventive Treatment

The cause of the degeneration of nigral dopaminergic neurons that occurs in Parkinson's disease is unknown. With the recognition of the selective neurotoxicity of MPTP, a likely cause seemed to be exposure to some ubiquitous environmental toxin, perhaps structurally similar to MPTP. Such exposure would not necessarily have had to occur immediately before the clinical onset of the disease, but may have occurred years earlier. Symptoms would not be expected to occur until the cumulative cell loss from exposure to such a toxin and to natural aging exceeded about 80% of the original cell population. No such toxins have been identified, however.

A widely held but not universal view currently relates the development of Parkinson's disease to endogenous toxins, such as free radicals, resulting from oxidation reactions (perhaps as a consequence of exposure to some exogenous environmental toxin).[48,49] More specifically, superoxide or hydroxyl radical formation from hydrogen peroxide may be important pathogenetically. In support of this hypothesis are the findings that the substantia nigra of patients with Parkinson's disease contains increased amounts of total and ferric iron, increased monoamine oxidase B activity, reduced glutathione levels, and diminished activity of enzymes involved in the breakdown of hydrogen peroxide and free radicals.[50] Exposure to free radicals leads to cell death by interaction with various cellular constituents. Their formation is promoted by the reduced form of iron, whereas glutathione is involved in the clearance of hydrogen peroxide from the brain. With age there is an increase in the presence and activity of striatal monoamine oxidase type B, the enzyme that leads to the oxidative deamination of dopamine.[51] An increased breakdown of dopamine enhances the formation of hydrogen peroxide, which may exceed the capacity of glutathione to clear it. The observations discussed earlier concerning the inhibition of mitochondrial complex I in MPTP-induced parkinsonism are of especial interest because mitochondrial complex I deficiency has also been reported in the substantia nigra of patients with Parkinson's disease.[52,53] Such mitochondrial abnormalities can be interpreted as a cause or product of oxidant stress.[48] At present, the evidence relating the pathogenesis of Parkinson's disease to damage by free radicals is circumstantial and compelling, but not conclusive.

Type B monoamine oxidase inhibitors or antioxidants such as vitamin E may protect against oxidative damage and thereby slow the progression of the disease. The role of selegiline in this regard has been examined in several studies, but especially in a large multicenter study in the United States.[54,55] This study showed that treatment with selegiline delayed the need to introduce levodopa as symptomatic therapy in patients with untreated parkinsonism. This was interpreted initially as evidence that the natural history of the disease had been altered, but it subsequently became apparent that selegiline itself exerted a mild symptomatic effect; accordingly, there remains some ambiguity about the basis of the effect that was observed.[56] Under these circumstances, it is difficult to formulate rational guidelines concerning its use, but it is my practice to prescribe selegiline to all patients making an informed decision to take the medication, unless they have end-stage disease or are of advanced age. It is taken in a standard dose of 5 mg with breakfast and 5 mg with lunch; such a regimen is not associated with the hypertensive or "cheese" effect of the nonselective monoamine oxidase inhibitors. It is important for patients to understand that the medication is not being taken for symptomatic benefit, that there is no way of knowing whether they are deriving any other benefit from it, that the medication will probably need to be continued indefinitely, and that its usefulness cannot be determined with certainty from the published studies. The evaluation of other inhibitors of monoamine oxidase type B, such as lazabemide, may be revealing.[57]

The multicenter study referred to earlier failed to find any protective benefit of vitamin E, 2,000 units daily, although tocopherol is an important scavenger of free radicals.[55] The extent to which this agent penetrates the brain is unclear, however.

Iron chelation therapy—to maintain iron in a relatively nonreactive state—has yet to be explored, but is another promising treatment avenue under study.

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NEUROLOGY *Therapy*

Guidelines for Treating Epilepsy in the Age of Felbamate, Vigabatrin, Lamotrigine, and Gabapentin

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For the first time in 15 years, new antiepileptic medications are available for the treatment of patients with seizure disorders. These drugs have demonstrated efficacy in animal models of epilepsy and in controlled clinical trials. Felbamate was licensed in 1993 for use as adjunctive therapy or monotherapy in adults with partial or tonic-clonic seizures and as adjunctive therapy for children with the Lennox-Gastaut syndrome. Gabapentin was approved January 1994 as adjunctive therapy in patients 12 years or older with partial seizures, with or without secondary generalization. Lamotrigine is expected to be approved this year for the treatment of partial and tonic-clonic seizures in adults. Last, a new drug application has been filed for vigabatrin this year, with possible licensing next year. These four anticonvulsants present new options in the treatment of patients with refractory epilepsy and are not merely congeners of previously available treatments. They have unique clinical spectrums and are reported to be safer and better tolerated than conventional therapy. Trials to compare their use with that of conventional therapy have not been done, and their use in the initial treatment of patients with epilepsy is not completely clear.

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Despite the optimal use of the currently available anticonvulsants, many patients' seizure disorders remain refractory to treatment, or they experience intolerable side effects. In 1987 it was estimated that of the 800,000 patients in this country with partial seizure disorders, about 360,000 were considered refractory to therapy.[1] More recently a Roper poll reported patients' experience with common epilepsy medications. Of the 760 patients answering a questionnaire, 63% had recurrent seizures, 61% suffered side effects, and 44% had both side effects and recurrent seizures.[2] When evaluated for their level of satisfaction with their current epilepsy therapy, 49% were unhappy about the side effects caused by their epilepsy medications and 59% felt they had no choice but to accept this level of seizure control and side effects. Clearly there is a need for more effective, better-tolerated anticonvulsants.

The most widely used anticonvulsants, carbamazepine, phenytoin, valproic acid, and phenobarbital (referred to in this article as conventional therapy), can be highly effective for certain patients. Each medication has its own spectrum of pharmacokinetic difficulties and troublesome side effects. Behavioral and cognitive changes are common with the use of phenobarbital. The nonlinear pharmacokinetics of phenytoin can pose challenges for a clinician. A narrow separation between doses that cause central nervous system side effects and those that control seizures (that is, small protective index—discussed later) is common to both phenytoin and carbamazepine.

Conventional anticonvulsants also frequently have non-central nervous system adverse effects for patients. The long-term use of phenytoin has been associated with coarse facies, acne, hirsutism, gingival hypertrophy, and peripheral neuropathy.[3] A rash occurs in 5% to 10% of patients taking carbamazepine, as well as hyponatremia and neutropenia. In rare cases, carbamazepine use has been associated with serious hematologic toxicity, including aplastic anemia and thrombocytopenia.[4] Taking valproate has been associated with gastric irritation, hair loss, weight gain, thrombocytopenia, inhibition of platelet function, and impaired hepatic function including fatal hepatotoxicity.[5] In addition to these direct side effects, conventional anticonvulsants also demonstrate major drug interactions that can produce substantial adverse effects or difficulties in administration.

Before the licensing of felbamate last fall, it had been 15 years since a new anticonvulsant was introduced in

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ABBREVIATIONS USED IN TEXT

FDA = Food and Drug Administration
GABA = γ-aminobutyric acid
MRI = magnetic resonance imaging

the United States. Gabapentin approval followed shortly (January 1994). Lamotrigine is expected to receive its final approval this year, and vigabatrin will probably be licensed for use in 1995. These four drugs represent anticonvulsants whose spectrum of action, side-effect profiles, and pharmacokinetics are substantially different from the anticonvulsants already licensed. In this article I will review these new anticonvulsants and make recommendations regarding their role in the treatment of patients with epilepsy.

Felbamate

Felbamate (Felbatol, Wallace Laboratories) was approved by the Food and Drug Administration (FDA) in 1993 for use as adjunctive or monotherapy in adults with partial seizures and as adjunctive therapy for the treatment of the Lennox-Gastaut syndrome in children. The mechanism of action of felbamate is not known. Felbamate demonstrates an anticonvulsant effect in models of seizure spread (maximal electroshock) and seizure threshold (pentylenetetrazol), with a spectrum similar to that for valproate but with a wider protective index—the ratio between the dose that produces toxicity in 50% of animals and the dose that inhibits seizures in 50% of the animals (Table 1).[6] Felbamate demonstrates a number of drug interactions, causing increases in the blood concentrations of phenytoin, valproate, and the epoxide metabolite of carbamazepine.[7] Side effects include insomnia, weight loss, and gastrointestinal complaints and infrequently require the drug to be discontinued.[8]

Several controlled clinical trials have demonstrated the efficacy of felbamate in the treatment of refractory partial seizures, and a double-blind, add-on trial proved felbamate effective in children with the Lennox-Gastaut syndrome. In addition to notable reductions of tonic, atonic, and atypical absence seizures, an assessment of the quality of life of treated patients showed substantial improvement.[9] Trials of felbamate in juvenile myoclonic epilepsy and infantile spasms have shown promising results.[10,11] Although the package insert gives dosing information for initial therapy in adults, felbamate has not been systematically studied in patients with newly diagnosed epilepsy.

In children the initial dose is usually 15 mg per kg of body weight daily in three divided doses with increases of 15 mg per kg weekly. The initial dose in adults is 400 mg three times a day, with weekly increases of 600 to 1,200 mg per day. Doses as high as 3,600 mg per day were used in the pivotal studies reported to the FDA, but doses of 4,800 mg per day or greater have been tried without serious side effects. When initiating felbamate therapy in patients taking carbamazepine, phenytoin, or valproate, the concomitant medication should be reduced by about 25%.

TABLE 1.—*Protective Indexes of the New Anticonvulsants (in Mice)*

Drug	Protective Index: Maximal Electroshock	Protective Index: Pentylenetetrazol
Phenytoin	6.3	NE
Carbamazepine	14.1	NE
Valproate	1.9	3.3
Ethosuximide	NE	4.4
Felbamate	38	20
Gabapentin	NA	NA
Lamotrigine	80	NE
Vigabatrin	NE	NE

NA = effective but median toxic dose not available, NE = not effective

Gabapentin

Gabapentin (Neurontin, Parke-Davis Pharmaceutical Research) was approved for use by the FDA early in 1994 as adjunctive therapy in patients 12 years of age or older with partial seizures with or without secondary generalization. It is water-soluble, has low toxicity, and is not metabolized by the liver, being excreted essentially unchanged by the kidney. It is not bound to plasma proteins, and no serious drug interactions have been described.[12] In studies of chronic toxicity, acinar cell adenocarcinomas of the pancreas developed in male rats.[13] The relevance of these tumors in male rats to carcinogenic risk in humans is unclear, as human pancreatic tumors are typically ductal in origin rather than of acinar cell origin.

The mechanism of action of gabapentin is not known. Gabapentin was synthesized as a structural analogue of γ-aminobutyric acid (GABA) that could penetrate the blood-brain barrier and mimic the actions of GABA in the brain. This is not the case, however. It has no effect on the concentration of GABA in the brain, is not metabolically converted to GABA or a GABA agonist, and does not interact with GABA receptors.[14] Gabapentin also does not show affinity for any of the other common receptor sites.

Gabapentin has demonstrated efficacy as adjunctive therapy in 5 controlled studies and 18 uncontrolled studies of patients with partial seizures that are medically refractory.[15] In these studies about 26% of the patients had a 50% or greater reduction in seizure frequency (Table 2).[16-19] Adverse events were usually mild in intensity and included somnolence, dizziness, ataxia, nystagmus, diplopia, and tremor.

Gabapentin is administered three times a day and is not affected by food. Typical dosages range between 900 and 1,800 mg per day and can be achieved within three days of initiating therapy. Dosage adjustments are required in patients with compromised renal function or in patients undergoing hemodialysis.

Lamotrigine

Lamotrigine (Lamictal, Burroughs Wellcome Company) is structurally unrelated to any existing epileptic drug and is a member of the phenyltriazine class. A new drug application was submitted to the FDA in December 1991, and approval is expected this year. It is already li-

TABLE 2.—*Controlled Trials of Anticonvulsant Drugs in Partial Epilepsy*

Drug	% Decrease	% Responders
Felbamate	23*	NA
Gabapentin	29	26
Lamotrigine	36	27
Vigabatrin	50	50
Carbamazepine	83†	52‡
Valproate	NA	73§

NA = not available

*A crossover trial.[16] †From Rodin et al.[17] Patients had complex partial seizures.
‡From Kutt et al.[18] §From Dean and Penry.[19]

censed for use in the United Kingdom, Ireland, Brazil, and Greece. Lamotrigine is a weak inhibitor of the enzyme dihydrofolate reductase in vitro and was screened for anticonvulsant activity when it was thought that antiepileptic drugs might act through an antifolate mechanism. In clinical studies, lamotrigine did not affect blood folate levels,[20] and pharmacologic studies suggest that lamotrigine acts at voltage-sensitive sodium channels to stabilize neural membranes and inhibit the release of excitatory amino acid neurotransmitters.[21]

Animal models of epilepsy suggested lamotrigine would have use in the treatment of partial seizures and generalized tonic-clonic seizures.[22] In controlled studies in humans, lamotrigine showed a dose-response efficacy, with about 33% of the patients having a 50% or greater decrease in seizure frequency.[23] The most frequently reported adverse events included dizziness, diplopia, headache, and ataxia. About 10% of patients experienced a rash.[24]

Lamotrigine is metabolized predominantly by glucuronic acid conjugation, and the inactive metabolite is eliminated by renal excretion. About 55% of the drug is bound to plasma proteins.[25] Although lamotrigine has no effect on the concentrations of conventional anticonvulsants, the reverse is not the case. In patients taking enzyme-inducing anticonvulsants (phenytoin, carbamazepine, or barbiturates), the elimination half-life is substantially decreased. In contrast, valproate significantly prolongs the elimination half-life of lamotrigine.[26]

Because of these considerable interactions, a complicated dosing schedule is required. The initial recommended dose of lamotrigine in patients receiving enzyme-inducing anticonvulsants is 50 mg twice a day, with increases of 100 mg each week. The maintenance dose ranges from 300 to 500 mg per day given in two doses. For patients receiving valproate, the recommended initial dose is 50 mg daily, with increases every two weeks to a maintenance dose of 100 to 200 mg per day. There is little experience in using lamotrigine in patients with either impaired renal or hepatic function. Because lamotrigine is extensively metabolized by the liver before excretion, caution should be used in such patients.

Vigabatrin

Vigabatrin (Sabril, Marion Merrell-Dow Inc) is the first of a new class of antiepileptic drugs that work by the selective, irreversible inhibition of GABA transaminase, the enzyme responsible for the metabolism of GABA. Cerebrospinal fluid measurements taken before and after treatment with vigabatrin in patients with medically refractory, complex partial seizures reveal a dose-dependent increase in total GABA, free GABA, and homocarnosine (histidine-GABA dipeptide) levels.[27]

Vigabatrin was undergoing clinical testing in the United States, but the trials were halted in 1983 when white matter degeneration occurred in mice, rats, and dogs.[28] The white matter changes (intramyelinic edema) were not associated with segmental demyelination and were reversible with the cessation of treatment. Patients with exposure to vigabatrin who subsequently underwent neurosurgical procedures and patients who died of other causes did not show these changes. In animals the white matter changes correlated with changes in magnetic resonance imaging (MRI) scans and sensory evoked potentials.[29] Laboratory tests including MRI scans and evoked potentials in humans undergoing treatment with vigabatrin have failed to elicit any evidence of serious systemic, neurologic, or neurophysiologic toxicity.[30] For these reasons clinical trials in the United States have resumed, and a new drug application is expected to be filed with the FDA in 1994. Vigabatrin is already marketed in 35 countries, predominantly in Europe.

Vigabatrin is neither protein-bound nor metabolized by the microsomal oxidase enzyme system. Vigabatrin could be given once or twice a day because of its prolonged pharmacodynamic effect; it is better tolerated on a three-times-a-day schedule. Few drug interactions have been reported with vigabatrin use, although a slight decrease in phenytoin levels has been described.[31] Vigabatrin is primarily eliminated by glomerular filtration, and therefore dosage adjustment will probably be necessary in patients with impaired renal function. Adverse effects appear to be infrequent and mild and include drowsiness, irritability, nervousness, dizziness, headache, or confusion. Less commonly reported side effects include weight gain and psychosis.[32] Despite the delay between the cessation of vigabatrin and the time required to resynthesize GABA transaminase, it appears that vigabatrin should be withdrawn slowly. A dramatic increase in seizures including status epilepticus has been described after vigabatrin was abruptly discontinued.[33]

Vigabatrin has been evaluated extensively in Europe and in the United States. Controlled multiple-dose trials of patients with refractory partial seizures found that about half of the patients had a 50% reduction in seizure frequency (Table 2). There was no increase in efficacy above 3 grams per day, but side effects were more common at the higher dose.[34] Trials of vigabatrin in children have been done only in Europe, and some efficacy has been found with partial and generalized seizures and the Lennox-Gastaut syndrome.[35] In children with infantile spasms refractory to corticotropin therapy, 75% have had a decrease in seizure frequency.[36] Increased seizure frequency with the use of vigabatrin has been reported in

patients with nonprogressive myoclonic epilepsy and absence seizures.[37]

Conventional Anticonvulsants

Previous controlled trials directly comparing phenytoin, carbamazepine, or valproate did not show one compound to be more efficacious than the others.[38,39] Therefore, when choosing an anticonvulsant, measures other than efficacy become important, including ease of administration, side-effects profile, and cost. The lessons learned from using conventional anticonvulsants also apply to the new anticonvulsants.

Direct comparisons among the new anticonvulsants or with conventional anticonvulsants have not been done, and there is no evidence to suggest one medication is superior to another. A double-blind trial of carbamazepine versus placebo was done in patients admitted to a hospital with intractable psychomotor epilepsy, and the secondarily generalized seizures were found to be decreased by 55% and the psychomotor seizures by 83%.[17] In a similar study, 52% of patients had a 50% decrease in seizure frequency.[18] Obviously, patients are considered refractory only when the available medications of the time have failed them. Patients in the carbamazepine trials had not been selected on the basis of failed trials of carbamazepine or valproate, and their seizures would possibly be less refractory than those in patients in recent trials. Similarly, of 30 patients with refractory complex partial seizures, 22 (73%) who were changed to valproate monotherapy had greater than a 50% reduction in seizure frequency.[19] Direct comparisons are difficult, but these studies do not clearly demonstrate a superiority for one anticonvulsant, conventional or new.

The new anticonvulsants have been priced to be comparable to valproate at the high end of cost. Phenytoin, because of its low cost (Table 3) and long half-life, allowing once-a-day dosing, should be the drug of choice for patients with partial seizures with and without secondary generalization. Because of gingival hypertrophy, hirsutism, and coarsening of facial features, however, carbamazepine replaces phenytoin in children. Despite the comparable efficacy in partial epilepsy, there is preliminary evidence that valproate is the drug of choice in patients with primary generalized epilepsies with spike-and-wave discharges in their electroencephalograms (Table 4).[40]

Of the new anticonvulsants, vigabatrin has had the most use to date and is being used as add-on therapy in Europe in patients whose initial treatment with carbamazepine or valproate failed to control their seizures. Considerably less information is available regarding the use of felbamate, gabapentin, and lamotrigine, but with increased patient exposures the ultimate role of these medications will be determined. All the new anticonvulsants show roughly equivalent efficacy against partial seizures with or without secondary generalization in patients whose seizures are uncontrolled by conventional medications. Lamotrigine may make patients with myoclonic seizures worse. In the Lennox-Gastaut syndrome, lamotrigine does not affect atonic or tonic seizures.[41] Felbamate, on the other hand, is effective in the Lennox-Gastaut syndrome.

TABLE 3.—*Name-Brand Anticonvulsants*

Drug	*Generic*	*Price, $**	*Typical Dose, mg/day*	*Cost/Day, $*
Dilantin . . .	Phenytoin	18.07	300-400	0.54-0.72
Tegretol . . .	Carbamazepine	34.66	600-1,200	1.04-2.08
Depakote . .	Divalproex sodium (valproate)	56.29	750-3,000	1.69-6.23
Felbatol . . .	Felbamate	66.00	2,400-3,600	2.64-3.96
Neurontin .	Gabapentin	90.04	900-1,800	2.70-5.40

*Average wholesale price January 1994 per 100 tablets.

Little evidence exists that helps physicians decide in which order to try these new agents. Based on experiments in animals and limited clinical experience, some suggestions can be made. Drugs with large protective indexes have a wider available dose range before toxicity is reached. Table 1 compares the protective indexes in two animal models for the conventional and new anticonvulsants. Using this approach, felbamate appears to have a therapeutic spectrum similar to that of valproate, with efficacy in treating partial, tonic-clonic, and absence seizures, but with a greater protective index. This has been confirmed in clinical trials. Felbamate has shown efficacy in both partial and generalized epilepsies with minimal toxicity. As predicted by the models, lamotrigine has a clinical spectrum similar to that of phenytoin, but with a wider "therapeutic window." Vigabatrin, on the other hand, demonstrates some efficacy in animal models of human epilepsy, but preliminary evidence suggests that some patients may have their absence seizures made worse by vigabatrin use.

To date, only one study has compared the use of a new anticonvulsant with that of conventional therapy. The use of vigabatrin was compared with that of carbamazepine in medically refractory patients with partial seizures. It showed a similar efficacy, but was slightly better tolerated.[42] Until controlled trials are done comparing the use of these drugs with that of conventional therapy in newly diagnosed patients, the use of the new anticonvulsants must be limited to medically refractory patients. In patients with juvenile myoclonic epilepsy or absence epilepsy refractory to valproate monotherapy, felbamate is probably the next medication to be tried. When vigabatrin becomes available, with its unique mechanism of action, it may have a role as rational polytherapy in patients with medically refractory epilepsy. Vigabatrin and gabapentin should be the easiest to prescribe because they lack drug interactions and have little protein binding. Gabapentin has the ability to be rapidly initiated and can be quickly tried in patients before their seizures are considered refractory.

These new anticonvulsants are reported to be safer and better tolerated than conventional therapy. This may indeed be the case; however, the limited human exposure may explain the lack of substantial allergic reactions. For

TABLE 4.—*Conventional and New Antiepileptic Drugs*

Generic Name	*Trade Name*	*Indications (Seizure Types)*	*Typical Dose, mg/day*	*Half-Life, hr*	*% Bound*	*Most Common Side Effects*
Phenytoin	Dilantin	Partial with or without seizure generalization; generalized tonic-clonic*	300-400	24-30	90	Gum hyperplasia, hirsutism
Carbamazepine	Tegretol	Partial with or without seizure generalization; generalized tonic-clonic*	600-1,200	8-12	75	Neutropenia, rash, hyponatremia
Phenobarbital	Luminal	Partial with or without seizure generalization; generalized tonic-clonic*	60-120	72	50	Behavioral changes
Divalproex sodium (valproate)	Depakote	Partial with or without seizure generalization; generalized tonic-clonic; absence; myoclonic*	750-3,000	6-12	90-95	Weight gain, hair loss, GI complaints
Felbamate	Felbatol	Partial with or without seizure generalization; generalized tonic-clonic; absence; myoclonic*	2,400-3,600	20-24	25	Insomnia, weight loss, GI complaints
Gabapentin	Neurontin	Partial with or without seizure generalization in patients >12 years old	900-1,800	5-6	0	Somnolence, dizziness
Lamotrigine	Lamictal	Pending†	300-700	24‡	55	Rash, dizziness
Vigabatrin	Sabril	Pending†	3,000-4,000	NA§	0	Drowsiness, irritability

GI = gastrointestinal, NA = not applicable

*Approved for use as monotherapy.

†Probably will be approved with indications similar to those for gabapentin.

‡Excretion half-life increases to about 72 hr with concomitant administration of valproate and decreases to about 13 hr when used with hepatic enzyme-inducing medications.

§Excretion half-life is not equal to pharmacodynamic half-life.

example, in the United States, approximately 275,000 people were taking valproate in 1993. The incidence of fatal hepatotoxicity is about 1 in 118,000 patients (all ages, as monotherapy).[43] By comparison, in the manufacturer's new drug application to the FDA, the exposure of 4,000 humans to felbamate was summarized. An absence of idiosyncratic drug reactions could be due to sampling error.

None of these drugs have demonstrated teratogenicity in animals, but there is no evidence suggesting that they are less harmful to a developing fetus than conventional anticonvulsants. Therefore, their use during pregnancy or in women of child-bearing age should be limited to women who have no other alternatives for seizure control.

Although the new anticonvulsants appear promising, physicians must not be swayed by intensive advertising campaigns or aggressive drug detail agents extolling the virtues of these new agents. The fascination clinicians have for new medications needs to be tempered by the uncertainties of unknown idiosyncratic drug reaction profiles, the limited database available on drug interactions, and the increased costs to patients.

Addendum

Since this article was submitted, the FDA in conjunction with Wallace Laboratories has recommended that patients be withdrawn from felbamate therapy. There have been ten cases of aplastic anemia, including two deaths, of a total of more than 100,000 patients taking felbamate. All of the cases of aplastic anemia appeared between two and six months after therapy was initiated. This incidence is about 50 times greater than that seen in the general population. The drug has not been recalled, but the FDA and Wallace Laboratories, as well as the Epilepsy Foundation of America, have recommended that the use of felbamate be suspended, unless the benefits of continued use clearly outweigh the possible risks. Unfortunately, sequential laboratory tests do not predict those patients who are at risk for this complication.

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NEUROLOGY *The New Era*

Neuroimaging Looks to the Future

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To discuss the future of neuroimaging, we have to consider the past and to assess how imaging now relates to the neuromanagement process.

In a typical medical center, neuroradiologic examinations constitute 40% to 60% of all computed tomographic (CT) scans and 70% to 80% of all magnetic resonance (MR) studies—including MR angiographic procedures. Neurovascular ultrasonographic and arteriographic examinations remain well used. Meanwhile, positron-emission tomography (PET), single photon-emission CT (SPECT), MR perfusion, MR diffusion, and MR spectroscopic imaging are being readied to illuminate clinically what once had been the darkest clinical recesses of the black box.[1,2]

This heavy emphasis on high-tech tools in the neurologic diagnosis-and-treatment process confronts and confounds health care planners. Health care economists tell us that society cannot afford open-ended neuroimaging access or use. Already in states where managed care has become predominant—for example, California and Massachusetts, where it accounts for 50% to 70% of services—the decision when to order what is being put increasingly in the hands of primary care physicians, who act as gatekeepers for imaging referrals in order to control imaging costs. Soon, however, with the growing movement toward capitation, the major part of the decision may be in the hands of the imagers themselves, who will have to decide how neuroimaging-assigned dollars are going to be spent. The effect of both trends no doubt will be to diminish the amount of neuroimaging activity, especially by obviating several imaging procedures in the same patient.

In this article I intend to put in perspective some of the reasons for the proliferation of neurodiagnostic tools and how clinical neuroscience (clinical neurology, neurosurgery, and neuroradiology) might respond to emerging efforts to ration neuroimaging services.

Background

Historically, the imperative in neurodiagnosis has been to "see" better what goes on within the skull and vertebral canal. In the 19th century the only way to penetrate the "black box" noninvasively was to devise a neurologic examination that allowed the location and extent of central nervous system injury to be inferred. Modern neuropathology began in the 1850s and 1860s, which spurred the development of the neurologic examination by facilitating the correlation of clinical neurologic findings with pathoanatomic processes. Signs and symptoms that were found to be associated with specific morbid lesions could then be used in vivo to predict diagnosis. This process received its initial major challenge in 1887, when a spinal tumor was first operated on, having been diagnosed and localized by deductive reasoning based on clinicopathologic correlations.

In that year W. R. Gowers saw a patient who had slowly progressive paraplegia and an ascending sensory level. Using information gathered from clinicopathologic correlation, he diagnosed a tumor in the vertebral canal, at the T-4 level, and advised its removal.[3] The lesion actually lay at the T-2 level and was almost missed. But the anatomically based speculations of those in the operating room resulted in the opening of the vertebral canal at successively higher levels until the tumor was identified. This operation was the first major test of the scientific method in clinical neuroscience. It demonstrated the capability of the neurologic examination to "see" with at least fair resolution beneath the skin and bony structures.

Within the next 40 to 50 years, actual imaging of central nervous system compartments became possible using radiographic techniques and contrast agents placed in the arteries (arteriography), ventricles of the brain (pneumoencephalography), and subarachnoid spaces of the spinal cord (myelography). But not until the development of CT a little more than 20 years ago could the brain or cord parenchyma be visualized directly. Lesions of these tissues previously had been inferred indirectly, based on radiologic changes in cerebrospinal fluid or vascular patterns. Evaluating parenchymal tissues was like looking at shadows thrown against a cave wall, rather than the sources of the shadows themselves. Because CT showed both parenchyma and intracranial cerebrospinal fluid spaces and did so noninvasively, it rapidly replaced pneumoencephalography. Some people predicted it also would replace arteriography. In fact, in the mid-1970s neuroradiology lost some of its luster as initial enthusiasm for CT engendered the illusion that arteriography would evaporate and that specialists might not be needed to interpret noninvasively obtained cross-sectional images that

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
MR = magnetic resonance
MRI = magnetic resonance imaging
PET = positron-emission tomography
SPECT = single photon-emission computed tomography

merely showed anatomy like any textbook. During this period I recall neuroradiology fellowship applicants questioning the future of the field.

Neuroradiologic Advances

The reasons why neuroradiology subsequently resurged include the following:

- The introduction of magnetic resonance imaging (MRI) with its high sensitivity, high resolution, and multiplanar capability;
- Technologic advances in all the imaging modalities, including CT, MR, ultrasonography, PET, and SPECT, which gave rise to an extensive array of imaging alternatives between and within modalities;
- The increasing capability for imaging not just anatomy, but also physiology;
- The persistence and refining of arteriography and digital subtraction angiography; and
- The evolution of interventional techniques, which made neuroradiology not just a diagnostic but a treatment specialty as well.

In sum, it again became obvious that the field had immense diagnostic resources, was operationally complex, and required persons with specialized skills. Moreover, for a decade and until recently, reimbursements for neuroimaging procedures skyrocketed. The more studies done, the more money earned. More than half the income of some departments of radiology came from neuroradiologic activities, so that general radiology was delighted to enhance neuroradiology's stature.

To the dismay of health care regulators, new methods or techniques do not necessarily supplant older ones, as the information they provide often is complementary, rather than redundant. Different imaging techniques typically demonstrate somewhat different features of anatomy or physiology. By creating a constellation of such discrete special data, a more precise diagnostic profile of disease can be provided. This is seen in the use of both CT (for calcification) and MRI in sorting out sellar region masses, MRI (T1-weighted to show subintimal blood) and MR angiography in clinching the diagnosis of arterial dissection, PET and MRI in identifying radiation necrosis, MR angiography and ultrasonography in documenting carotid disease, and CT (for hematoma) and MRI (for abnormal flow voids) in demonstrating hemorrhage from an arteriovenous malformation. The prototypical example of a multimodality battery is the use of direct and indirect tests in carotid ultrasonographic noninvasive diagnosis, where as many as seven high-tech examinations might be used to sample different levels of the vascular axis and different physiologic features at each level. In general, as instruments improve, so do the quality of the pathoanatomic and pathophysiologic data and the reliability of diagnosis. If the current pace of technologic progress in neuroradiology continues, in the future we might expect to find batteries of neuroimaging procedures routinely used not just for diagnosis, but to monitor tissue events that herald clinical improvement or deterioration—that is, to help plan or monitor on-line treatment. Technologic advances typically increase the reach of clinicians, which in some situations exceeds the grasp of any one instrument or technique.

Current Role of Neuroimaging

Neuroimaging is no longer an exercise remote from clinical medicine, but has become an extension of clinicians' eyes, ears, and fingers. Computed tomography and MRI often can localize lesions better than a neurologic examination, and Doppler testing can assess turbulent flow better than a stethoscope. Special procedures are now used not just to confirm or reject the "bedside" formulation (Table 1), but in many cases to complete it. Even with most routine diagnostic problems, I believe that if a neurologist examines a patient to rule out disease of the cerebral hemispheres, that examination is not complete unless at least a CT scan is done. A CT scan can be done only a little less quickly than it may take to figure out, for example, if the plantar response is up, down, or withdrawal, and it provides another dimension of information.

TABLE 1.—*Neuroimaging Before and After the 1970s*

Neuroimaging	
Before 1970s	*After 1970s*
Primarily invasive	Primarily noninvasive
Assesses anatomy	Assesses anatomy and physiology
Abets diagnosis	Abets diagnosis and treatment
Confirms bedside formulation	Completes bedside formulation

An imaging study can provide unexpected information that can obviate considerable morbidity for a patient and, as a result of early detection, reduce costs for the health care system. For example, in patients with normal neurologic findings, we have seen meningiomas, subdural hematomas, and temporal lobe neoplasms as the causes, respectively, of depression, transient ischemic attacks, and the hyperventilation syndrome. To emphasize the importance of imaging is not to minimize the role of the neurologic examination itself, but rather to say that some imaging studies are better thought of as the last step in the neurologic examination, rather than the first step in the special-procedure workup. Moreover, imaging studies cannot be effectively interpreted without the history and examination that constitute the neurologic evaluation. In fact, technologic advancements may increase the need for better history-taking and mental status assessments.[4]

Just as neurologists choose the bedside tools they will use to answer a clinical question, someone also needs to select the appropriate battery of imaging modalities and

choose from among the techniques available for each modality. Some time ago we pointed out that to ensure the choice of the correct imaging study and its appropriate mode of application, a subset of "new clinicians" might be required—persons trained in both clinical and technologic areas and in the monitoring of function as well as structure.[5] As both a neurologist and neuroradiologist, I use this approach in our Neurovascular Laboratory (which does carotid and intracranial ultrasonographic evaluations), where as many as 13 different clinical (5) and technical (8) examinations may be carried out primarily by a physician. At any moment the physician can alter the examining battery of tests according to the clinical imperatives and the emerging medical and technologic information. This is similar to the process at the "bedside," where the priorities of the examination are constantly altered as a result of the emerging data.

These comments are not intended to bear upon the debate as to whether neurologists or neuroradiologists are better prepared to do and interpret imaging studies or be the new clinicians. At this time few in either field entirely fit the latter description. Neuroradiologists have a better understanding of underlying anatomy, physics, techniques, and range of normal, and neurologists better understand the clinical and possibly the pathophysiologic processes. Both have a body of knowledge to share and must work together to ensure that neuroimaging remains dynamic and focused on patient care. For the two fields to challenge each other, especially in a hostile health care environment, makes no sense and is not justified. If neurologists, for example, complain that neuroradiology has locked them out, they may share some of the blame.

In the 1970s many major academic neurology programs that served as national prototypes became relatively indifferent to the need for neuroradiology training for their residents. During the latter part of that decade, the Massachusetts General Hospital (Boston) Neurology Service, for example, dropped its mandatory full-time neuroradiology rotation to offer additional elective time, particularly basic science research opportunities. Whereas during my neurology senior residency at that center from 1969 to 1970, we had a month-long rotation during which we alternated with neurosurgical residents in performing almost all the arteriographic, pneumoencephalographic, and myelographic procedures, neuroradiology now became an elective, and an undersubscribed one. Those who took the rotation, however, had the opportunity to participate in writing the protocols for the day's head CT scans and in interpreting, dictating, and signing the completed studies. On the days I supervised head CT scans, the neurology resident often was so burdened with clinical neurologic or research responsibilities that only occasionally did he or she show up. As a result, neurology residents eventually lost the opportunity to read head CT scans. Similarly, direct carotid punctures and brachial angiograms were not taken away from neurologists at Massachusetts General Hospital. The neurology residents stopped doing them because of a higher complication rate.

To preserve the availability and maintain the progress of neuroimaging, clinical neuroscience must take a cohesive stand. If primary care physicians become the gatekeepers for neuroimaging procedures, access to these tools will be limited. Primary care physicians have a modicum of neurologic training and virtually no neuroimaging experience. For them to order or authorize imaging procedures seems hardly different from having them ordering or authorizing a neurologist to use an ophthalmoscope or reflex hammer or to check for parietal cortical sensory loss. It would be difficult for them to know which imaging tools are appropriate. For example, how to assess the neurovascular system has become a confusing process even for neurologists and neuroradiologists who do not work with the problem every day. When to use or combine ultrasonography, MR angiography, spiral CT angiography, and x-ray arteriography in examining the vascular substrate of ischemic stroke disease can be a difficult question.[6-8] The first three tests all now qualify as "noninvasive studies." Each test cannot be done in every person. Yet, more than one test may be necessary to make correct management decisions.

Effects of Capitation on Neuroimaging

If full capitation becomes a reality, the effects on clinical neuroscience and neuroimaging also will be great, but from a different point of view. Maintaining large neuroradiologic facilities suddenly may become a liability for radiology departments. This could result in a downsizing of neuroimaging in general or at least a pronounced limitation on complementary or ancillary studies that now are relied on to help clarify the findings of an initial examination. Paradoxically, some of this may be beneficial. It will cause neurologists, neurosurgeons, and neuroradiologists to examine which imaging studies are actually necessary and will stimulate outcome studies to accomplish this. Moreover, it will require neurologists to educate primary care physicians as to when to refer a patient for a neurologic consultation or neuroimaging procedure.

A "catch 22" situation may be brewing. Although neurologists will want to have the responsibility of deciding on and ordering imaging studies, under managed care programs neurologists who order "too many" studies may be stigmatized by health care agencies as expensive physicians, a label that might cause health maintenance organizations to limit the number of subsequent referrals.

To deal with neurodiagnostic issues in the future, I recommend a standing group of neurologists, neurosurgeons, and neuroradiologists who will help establish imaging policies for clinical neuroscience, rather than having policy dictated to the specialists. Among the pressing issues are the following:

- Deciding which imaging procedures are required in which situations.
- Organizing appropriate investigations to clarify which test or constellation of tests is optimal for clinical care; a position paper of the American College of Physicians has recently criticized the limited number and poor quality of outcome investigations for MR imaging.[9]

TABLE 2.—*Cost of Neurovascular Studies (Technical Plus Professional), Sampled From Selected Geographically Separated Institutions*

Study	*Cost Range, $*	*High Versus Low**
MR angiogram, neck or head	414-2,696	6.51
Bilateral neck or head arteriogram	1,146-3,822	3.34
Transcranial Doppler examination	213-679	3.19
Carotid ultrasonogram	396-820	2.07
Spiral CT angiogram, neck	725-1,289	1.78
Spiral CT angiogram, head	618-816	1.32
Total for least/most expensive institutions	3,512-10,122	2.88

CT = computed tomography, MR = magnetic resonance

*How many times greater the most expensive institution is relative to the least expensive.

- Establishing standards of quality for doing imaging procedures to ensure that the drive toward economy will not erode the high level of neuroradiologic activities.
- Exploring how neuroimaging services can be rendered as reasonably as possible so that more comprehensive evaluations can be accomplished within a limited budget. The wide range of neuroimaging charges today is exemplified by the costs of carotid noninvasive ultrasonographic studies determined for six randomly selected institutions across the country (Table 2).
- Developing appropriate programs to train new clinicians. For board-eligible or -certified neurologists or neurosurgeons who want to do neuroimaging, it might be appropriate for neuroradiology to offer a 3-year training program that consists of the usual 2-year program with 12 additional months of radiologic interpretation, physics, and imaging. No such program should limit neuroimaging training to just CT and MR. Doing so would deprive trainees of a rich resource of clinically important neurodiagnostic tools.

Plato, in *The Republic* (Book VII), presents a parable that with imagination (in brackets) may be applicable to this problem:

Behold human beings chained in an underground cave so that they can only see before them. Above and behind is a fire blazing. . . . Do you think they have seen anything of the figures passing in front of the fire except the shadows which the fire throws on the opposite wall of the cave? To them the truth would be literally nothing but the flickering shadows *[compare neuroradiology before CT]*. These men might have been in the habit of conferring honors among themselves, on those who were the quickest to remark which of the shadows went before, which followed after, and which were together *[compare reading an arteriogram]*, and being best able from these observations to divine the future *[make a diagnosis]*. . . .

Imagine one of these men being reluctantly dragged into the presence of the sun itself *[CT or MRI, which demonstrates brain tissue itself]* and then coming down suddenly and being replaced in his old seat; would he not be certain to have his eyes full of darkness? And if there were now a contest and he to compete in measuring the shadows with the prisoners who had never been moved out of the cave, would he not make himself ridiculous? Men would say of him that he had returned from the place above with his eyes ruined. *[Those who focus too closely on CT or MRI may lose the ability to interpret critical details provided by other neurodiagnostic methods, including the clinical evaluation.]*

I have tried to highlight two trends: the historical expansion of neurodiagnostic techniques to better "see" pathoanatomic and pathophysiologic change, and a more recent emphasis on greater selectivity in requesting and performing neuroimaging studies to limit health care costs. The two need clash only if the clinical neurosciences cannot eventually justify the use of high-tech, multimodality imaging studies in achieving better diagnosis and patient care, and if primary care physicians or health care planners refuse to appreciate the complexity of the clinical and special-procedure neurodiagnostic processes and how profoundly interdependent they are.

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NEUROLOGY *The New Era*

Neurologic Education

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Medicine is in a state of rapid flux. In the next few years and the first decades of the 21st century, we will see rapid and profound changes in health care delivery in the United States. How will these changes affect neurology and neurologists, and how will they affect neurologic education? After briefly reviewing the current state of neurologic education and future changes that will influence it, we shall concentrate on how neurologic education can and should change to adapt to and meet these new educational needs and imperatives. The literature on this subject is scant, so of necessity we will present a personal viewpoint that may not represent that of most neurologists.

Status

Neurologic education clearly does not meet the present needs of medical students and nonneurologists. Nearly all medical students in the United States have one or more courses during the first two years of medical school in the basic neurologic sciences—neuroanatomy, neuropathology, neurophysiology, neurochemistry. Sometimes the various disciplines are taught separately and sometimes they are integrated into a single neuroscience course. The combinations of disciplines in a neuroscience course vary; most often anatomy and physiology are combined, but pharmacology and pathology are sometimes included. The clinical neurology faculty sometimes directs or has considerable influence over the content of neuroscience courses; often, however, the courses are controlled by basic science faculty with little involvement of the clinical neurology faculty. Broadening of the curriculum and early entry into the clinics and bedside medicine have drastically reduced the time medical students spend in basic neuroscience.

Because funded research among basic science faculty has become almost exclusively molecular and cellular, few faculty members are interested and knowledgeable in classic gross neuroanatomy, neuropathology, and neurophysiology. Much of the curriculum concentrates on the cellular microscopic level, and instruction in macroscopic aspects has dwindled. Yet the gross aspects of neuroscience are and will continue to be the foundation of neurologic practice in the foreseeable future. The vast majority of American medical students do not get sufficient education in nervous system anatomy, pathology, and physiology. Some students do, however, get "turned on" by the most complex and arguably the most important and intriguing organ system in the human body.

Neurologic education during the third and fourth clinical years of a medical school curriculum is even worse. Levitt found, in a 1978 survey, that fewer than half of graduating students in Philadelphia medical schools had a neurology rotation.[1] Similarly, in the United Kingdom, where there are more data, at least a third of medical schools had no instruction in neurology during the clinical years.[2] Some medical schools require a clinical neurology rotation—usually four to six weeks—but many do not, and neurology is instead an elective subject. In some schools, the neurology rotation is diluted by rehabilitation, ophthalmology, and other disciplines. Four weeks is scarcely enough exposure to whet the appetite, much less get the feet wet with useful experience.

The clinical neurology rotation is usually on inpatient service, which now has a select group of the sickest patients who are herded through quickly. Medical students are usually simply appended to the team of neurology residents and fellows and rotators from other services such as internal medicine, family practice, and psychiatry. The service is usually led by a busy clinician or research scientist. These instructors usually have insufficient time and interest in teaching the medical students, clearly the lowest group on the totem pole and the most difficult and time-consuming to teach. Little time is spent on outpatient care despite the fact that most clinical neurology relates to ambulatory patients. Seldom are the medical students taught separately.

In many clinical neurology rotations, there is no standard curriculum, bibliography, expectations, or evaluation system. Education of medical students is a low priority for most faculty and little economic remuneration, academic promotion, or departmental kudos derive from diligence and time spent in this activity. Neurologic education of medical students gets a C− at best. Fortunately, despite the system, a precious few, especially those who were attracted to neuroscience during their premedical education, enter neurology training programs. Some pur-

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sue neurology because of the subject matter and discipline of the specialty; some are attracted by the role models they encounter and seek to emulate.

Neurologic education of nonneurology house staff is also inadequate. Few general physicians—family practitioners, internists, pediatricians, obstetrician-gynecologists—know much neurology when they enter practice. Levitt's 1978 survey indicated that about a fourth of all patients admitted to Philadelphia hospitals had important neurologic problems and a fifth of patients' first visits to representative general internists included a neurologic complaint. Despite this large burden of neurologic disease, graduates of internal medicine residencies spent only about 3% of their residency in neurology, and many had no instruction in neurology.[1] Now, virtually all emergency department and inpatient neurologic treatment is being provided by neurologists. The competency level of generalists handling neurologic problems is frighteningly low.

In the past decade the neurologic education of nonneurologists has shifted.[3-4] Family practice programs are increasingly desirous of neurology experience for their trainees, and many programs have enunciated guidelines on neurology curriculum for family practice residents.[5] About four fifths of family practice programs have a defined neurology rotation, usually in the form of a preceptorship with a community-based neurologist.[4] Of the neurologic training of family practice residents, 75% is in the community and the rest is on traditional university neurology inpatient units.[4] Core neurologic content is most often presented through lectures and assigned reading, with less teaching and experience that involve hands-on bedside interactions. In contrast, internal medicine residents are increasingly occupied with ill patients with cancer, the acquired immunodeficiency syndrome and other infections, and heart disease. Little time and less interest are available for neurology. Only in institutions where there is no formal training program in neurology do generalists get much training or experience with neurologic problems. Neurology education of nonneurologists gets about a C, but family practice and psychiatry residents now want and receive more neurology training than in the past.

Changes, Directions, and Stresses

In the future, patients will almost surely have a larger burden of neurologic problems. Increased life expectancy means more geriatric patients with degenerative disorders such as cerebrovascular disease, dementia, and Parkinson's disease. At the other end of the age spectrum, more premature and neurologically impaired neonates and infants now survive with complex and severe nervous system problems and handicaps. Our violent times result in more brain and spinal cord injuries.

The technology used to diagnose and treat patients with nervous system disease is changing dramatically. Could neurologists of the past generation have even dreamed of computed tomography and magnetic resonance imaging, of modern ultrasonography, of single-fiber electromyograms, of stereoscopic probes, angioplasty, focused radiation, and interventional radiology? More can be done, but the knowledge and training required to use these powerful diagnostic and therapeutic tools are becoming ever more specific and specialized.

Economic and societal pressures dictate changes in personnel and activity. By 2010, there will be fewer specialists and more generalists; less hospital-based care, more outpatient and community-based care; fewer subspecialists; tighter money and control, more restrictions and patient-care protocols; more nonphysician providers of health care; and more health maintenance organizations and group practices—more managed care—and fewer solo or small group practices.

Another important factor in the future of education is the ubiquitous computer. Computer capabilities ease the burden of required memory and rote knowledge and offer the opportunity for students and practitioners to quickly gain access to a large body of knowledge. Training future practitioners to manage the ever-growing mass of data is a challenge, but computers offer a wonderful opportunity that to some extent offsets the sophistication needed to handle the increasing burden of illness and complexity of diagnosis and treatment.

The forthcoming changes mean that fewer patients with neurologic problems will be cared for only by neurologists, as is now the usual practice in many areas of the United States. Patients with neurologic symptoms will be required to first see or call primary care physicians or, in some programs, less expensive nonphysicians who will use protocols and guidelines for gatekeeping. According to Griggs and Dickinson, the "neurologist's principal role is to serve as a consultant to primary care physicians and their patients."[3(p719)] There will likely be fewer available neurologists who will have less time and be constrained to use less expensive technology to care for a broader range of neurology patients. The situation will more closely resemble the present status of neurologists in most of Europe. Both primary care physicians and nonphysicians and neurologists will need different and better training to fulfill these new roles.

Teaching Neurology

Basic Neuroscience

The newer diagnostic capabilities of imaging the brain and spinal cord and their vascular supply make it even more imperative that students and practitioners know neuroanatomy and neuropathology. Scans and vascular studies cannot be intelligently ordered or their findings understood without knowing what the structures that are shown look like in healthy persons and in patients with various diseases. Because clinical testing is so divergent and depends on the level of involvement—muscle, peripheral nerves, spinal cord, brain stem, cerebrum—students and practitioners will need to know some neurophysiology to understand these levels of involvement. To teach the basic foundation subjects, more time must be spent on gross neuroanatomy, neurophysiology, and neuropathology. Microscopic and molecular aspects can be taught in a separate course on general molecular biology, with

TABLE 1.—*Basic Neuroscience for Medical Students in Preclinical Years*

Adequate time for the course—a minimum of 12 weeks
Integrated neuroanatomy, neuropathology, neurophysiology, and neurochemistry
Focus on application of basic science to patient problems
Use of computers to aid instruction; heavy use of patient materials
Integration of the approach to problem solving in neurology patients
Patient demonstrations—live or by videotape
Practical examinations using anatomic and pathologic figures and patient example questions
Use of computed tomographic and magnetic resonance imaging depictions of normal and abnormal anatomy

some aspects integrated into the neuroscience course that will likely prove useful for practitioners. Suggestions for the basic course are listed in Table 1.

Although computers are useful as devices for reviewing neuroanatomy, they are less well suited for primary instruction. Computers do offer an excellent way of showing numerous sections of the body serially, and together with three-dimensional reconstructions they facilitate a three-dimensional appreciation of such structures as the fornix and the ventricular system. With the number of autopsies continuing to shrink, digitized images of brain slices are replacing dissections as a way to understand the internal structure of the brain.

Clinical Neurology Rotations

Neurology must become a required rotation for all medical students. A clerkship should be for a minimum of four to six weeks, undiluted by other responsibilities. We espouse the goals listed by Wilkinson for the clinical rotation (Table 2).[2] A staff preceptor will be assigned who will supervise, teach, and evaluate students' performance. The preceptor and students should meet separately from the house officers on the service. At the beginning of the rotation, the students should be given curricular expectations and a short eclectic bibliography. Students should have exposure to outpatient neurology during the rotation.

One problem in instituting required clerkships in neurology is the need to repeat instruction in basic subjects such as headache, dementia, and epilepsy for each group of students, that is, 12 times a year. In addition, at many medical schools clinical rotations are held at more than one hospital, making a standard educational experience difficult. Videotapes of standard presentations on basic subjects can be used to supplement instruction, to be followed by discussion with the attending staff. Video conferences would allow students at distant sites to see presentations at conferences such as neurology grand rounds at a main campus.

TABLE 2.—*Clinical Attachment—Learning Objectives of Clinical Rotations**

Learn the techniques of neurologic examination
Practice the neurologic examination on enough patients to ensure confidence
Become familiar with the common neurologic disorders—stroke, dementia, headache, seizures, Parkinson's disease, neuropathies
Have adequate exposure to patients with these common disorders
Discuss management of the serious neurologic emergencies—coma, uncontrolled seizures, spinal cord compression, acute stroke, severe neuromuscular paralysis
Have exposure to patients with neurologic emergencies
Become able to integrate the symptoms and signs in patients with neurologic diseases into a differential diagnosis and plan of evaluation and treatment

*From Wilkinson.[2]

Students should learn to obtain an adequate, detailed neurologic history, to do a thorough neurologic examination, and to begin to organize the findings so that they can present a reasonable differential diagnosis and plan of investigation and treatment. The faculty preceptor should, during the rotation, observe the students' encounter with patients, including the examinations. Optimally, at the end of the rotation, the students should be given an examination (oral or written) using mostly patient-oriented queries about common neurologic diseases.

TABLE 3.—*Management of Neurologic Disorders by Primary Care Physicians and Neurologists*

Primary Care Physicians	*Neurologists*
Headaches	Brain tumors
Some dementias*	Strokes and cerebrovascular disease
Some neuropathies*	Epilepsy
Some patients after head injury	Movement disorders
Stable childhood encephalopathies	Parkinson's disease
Neck and back pain	Complex degenerative diseases
Chronic pain	Most neuromuscular diseases
Syncope	Myasthenia gravis
	Multiple sclerosis
	Central nervous system infections
	Coma
	Encephalopathies
	Stroke
	Spinal cord disease
	Acute neuromuscular diseases
	Nerve root lesions

*Especially if patient is stable, diagnosis is known, and no active, complex treatment is needed.

Nonneurology House Staff

In the future, interns, residents, and fellows from so-called primary care specialties will spend more time on neurology rotations. For the rotation to be successful, the goals should be realistic and modest. Primary care physicians simply cannot be trained to care competently for most patients with nervous system disease. The emphasis should be on when and how urgently to seek neurologic consultation; managing neurologic emergencies; learning to take a detailed, relevant neurologic history and do a neurologic examination; learning the common neurologic tests and their indications, risks, and major limitations; and recognizing neurologic complications of medical illness.

Primary care practices will be heavily weighted to-

ward outpatient care. Moreover, most neurologic problems that primary care physicians see and manage will be in outpatient settings. In a hospital, primary care physicians will surely have access to neurologists and will rarely treat serious neurologic problems without consultation. For these reasons, outpatient experience under the direction of experienced neurologists is important. This experience can be scheduled during the neurology rotation. Another excellent way to provide this education will be to have a neurologist available at the outpatient primary care site to instruct generalists on the neurologic problems of their patients.

Those training in primary care should be given a curriculum and bibliography emphasizing the common diseases they will see in practice. We have listed in Table 3 which disorders primary care physicians will likely manage and those that should be managed by neurologists. A minimum of two to three months should be spent on neurology training. A rotation at different times in the training, such as first and third years, helps emphasize and reinforce the teaching. Also, during the year, patients with neurologic problems should be discussed by neurologists at the teaching rounds of the primary care services. Computer programs should be available that briefly summarize information about the major neurologic diseases with a few references. Decision trees are also helpful for evaluation and management.

Conclusion

The burden of neurologic illness is increasing and will continue to increase in the foreseeable future. New technologies will facilitate neurologic evaluation, and new therapies will become available. Patients and families now and in the future will have increased expectations that physicians will be able to treat and help their neurologic problems. In the future the vast bulk of neurologic problems will be brought first to generalists and primary care physicians. These physicians must have exposure to neurology and effective training if they are to appropriately manage, and refer patients with neurologic complaints and findings. All phases of medical education and training should include neurologic exposure. The neurologic teaching must be thorough, problem-based, and practical and should include instruction in obtaining and using information quickly and effectively.

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Neurorehabilitation

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Neurorehabilitation is a relatively recent concept and did not become an issue until after World War II. Many of the casualties of that war who suffered spinal cord and head injury avoided death from infection by receiving antibiotics, and the survivors needed help to regain some degree of independence. Antibiotics also made it possible for persons who had suffered serious stroke to survive infectious complications such as pneumonia and urinary tract infection. This has left a large number of persons living with serious physical disability.

Physical disability caused by neurologic disease is the most common reason for admitting patients to a rehabilitation hospital. The conditions that are most frequently encountered on a neurorehabilitation service are stroke, traumatic head injury, spinal cord injury, multiple sclerosis, Parkinson's disease, and devastating peripheral neuropathies such as the Guillain-Barré syndrome. Patients with these conditions usually account for about two thirds of the patients in any modern rehabilitation hospital. These problems are neurologic, but in the past they have been managed largely by physiatrists. The scope of the problem of neurologic disability has enlarged with the development of physical medicine and rehabilitation programs that were heavily focused on patients with spinal cord injury.

Neurorehabilitation has become more complicated, and the level of intensity of care provided has increased, so it is important that neurologists assume more responsibility for the long-term management of these patients. Care for patients who need inpatient rehabilitation from physical disability caused by a neurologic illness requires a team of professionals with special skills including physical, occupational, and speech therapists, rehabilitation nurses, social workers, guidance counselors, and peer counselors. Managing all of these activities becomes the responsibility of the physician in charge.

There is no evidence that programs of rehabilitation have any effect on restoring impaired nervous system function or enhancing natural recovery following disease or injury. These programs do improve patients' ability to perform daily activities and self-care and to achieve functional independence. The scope of the problems of neurorehabilitation is best presented by a brief review of the usual conditions that are thought suitable for treatment.

Cerebrovascular Disease

Stroke is the most common cause of physical disability in persons older than 60 years, and 40% of all stroke survivors require inpatient rehabilitation care. In the United States, 500,000 to 600,000 new strokes occur every year. With the current mortality rate running about 20% to 25%, this leaves a large group of persons with physical disability.

Stroke is the most common reason for the admission of adults to neurorehabilitation services. The cause of the stroke does not dictate treatment; the focus of treatment is on the functional deficit, most commonly hemiparesis or hemiplegia. The number of patients who are suitable for stroke rehabilitation is not large. In an analysis of this problem at the Burke Rehabilitation Hospital of Cornell University Medical College (White Plains, NY), only about a third of patients with stroke were suitable for inpatient rehabilitative care. About 20% of persons with stroke will die, and 10% will recover so completely that they have no need for rehabilitative services. This leaves approximately 70% who have substantial physical disability that requires rehabilitation. Of this 70%, about 10% will be so functional that they can be managed adequately as outpatients. Half of the remainder will be so devastated by the severity of the stroke or have such a decline in intellectual capacity or comorbidity from heart disease that they are unable to engage in rehabilitation programs. This leaves approximately a third of the victims of stroke as suitable candidates for admission for acute rehabilitation. Similar data have been reported from England, where it was found that only about 12% to 15% of patients with stroke were suitable candidates for inpatient rehabilitation.

Programs of inpatient rehabilitation are designed to teach patients how to manage with their remaining intact function and become as independent as possible. Such programs depend on the ability of the stroke survivor to learn. In the most uncomplicated situation, this means that if someone has a left cerebral infarct and a right hemiplegia, the patient must learn how to be left-handed. Other problems for patients in inpatient rehabilitation services include the frequent comorbidity from other organ systems affected by generalized atherosclerotic vascular disease in the heart and peripheral vessels. These conditions often are as serious or more so than stroke.

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Most commonly a person who enters a rehabilitation program after having a stroke has some degree of hemiparesis. The arm and hand are almost always more severely affected than the leg. Generally there is some return of function in the lower extremities, more often proximally than distally.[1] This makes it possible for suitable orthotic devices to help patients walk.

The chances of successfully rehabilitating a person with stroke vary widely, and goals must be based on the degree of neurologic impairment. In studies by Reding and Potes, persons with only motor involvement had the best outcome, when judged by the ability to walk 46 m (150 ft) without assistance or to attain self-care as measured by the Barthel Index.[2] For patients who also had a sensory deficit, the chances of reaching these goals declined (Figure 1). If the patient had motor involvement, sensory involvement, and hemianopsia, the chance of attaining these goals was limited. Reducing the goals to walking with assistance and achieving a marginal ability for self-care, those patients with only motor involvement had the best chance for improvement, but those with motor, sensory, and visual involvement often could achieve these goals if they were kept in rehabilitation programs long enough (Figure 2). Improvement following stroke occurs in the first three months (Figure 3).[3,4] Further improvement may occur after three months, but it is generally less notable.

Questions are often raised about whether dedicated stroke rehabilitation units are desirable.[5,6] The evidence is fairly good that staff who are expert in dealing with patients who have had strokes can anticipate patients' problems and prevent them from becoming serious. Dedicated stroke units also provide a cadre of patients who set an example for newly admitted patients about what can be accomplished with stroke rehabilitation. In most inpatient stroke rehabilitation programs, about 95% of the patients are able to return home, usually with minimal assistance from care givers. In follow-up studies, the improvement has been sustained.

Head Injury

The number of patients requiring rehabilitation after head injury is difficult to determine because head injury

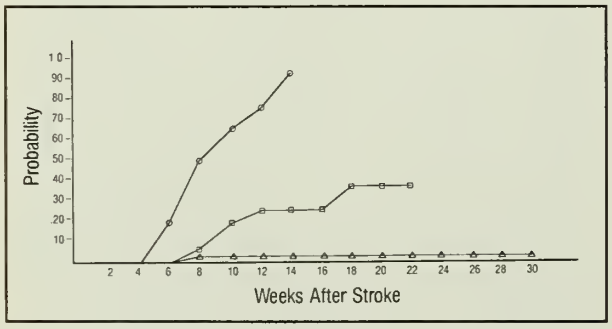

Figure 1.—The time course and probability of walking 46 m (150 ft) or more without assistance are shown for patients with motor deficit only (○), those with motor and sensory deficits (□), and those with sensory and visual deficits (△) following stroke (from Reding and Potes[2]).

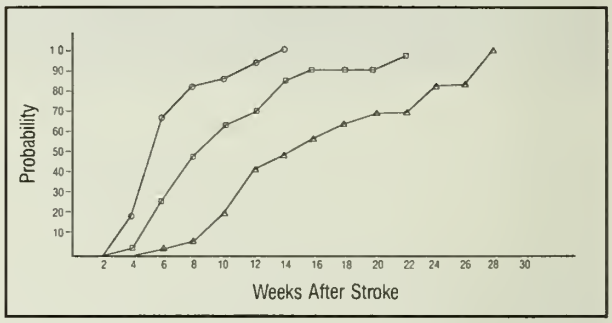

Figure 2.—The time course and probability of walking 46 m (150 ft) or more with assistance are shown for patients with motor deficit only (○), those with motor and sensory deficits (□), and those with sensory and visual deficits (△) following stroke (from Reding and Potes[2]).

is not always coded in medical records according to the degree of severity. The incidence of head injury is thought to be about 200 per 100,000 population, with a death rate of 10% to 20% and a prevalence of 400 per 100,000.[7] About 10% to 20% of persons who have a diagnosis of head injury made in an emergency department are estimated to have brain damage serious enough to require some form of rehabilitation. This group of patients is of considerable importance because head injury is most likely to occur in younger persons. Those who survive a head injury often will require lifelong public assistance and physical help to manage disability and intellectual impairment. This puts an enormous burden on families and social organizations.

Head injury almost always causes not only physical disability and intellectual disability but also personality change. It is often accompanied by many serious orthopedic problems. In young persons neurologic and cognitive improvement is likely, but striking improvement is uncommon in older victims. Intellectual impairment and personality change are the most difficult problems to manage in head injury rehabilitation.[8-10] Patients in coma following injury need ongoing rehabilitative care, especially passive range-of-motion exercises to avoid contracture. Coma stimulation programs have been tried without good evidence of effectiveness, and their specificity is almost impossible to determine because of the background noise coming from the almost constant nonspecific stimulation that occurs in patients in a hospital. The management of patients with motor deficits is similar to that of patients with stroke and consists of strengthening remaining function and providing education in using intact function to improve patients' ability to perform their daily activities.

Programs that deal with cognitive impairment are directed toward behavior modification, relearning social skills, and adapting patients to reduced intellectual levels. Specific cognitive rehabilitation techniques directed at memory and behavior improvement are in use. They have shown some effect on specific problems such as memory loss, but this improvement is not always applicable to other aspects of cognition and behavior.[11] Patients with serious behavior problems often need hospital stays with

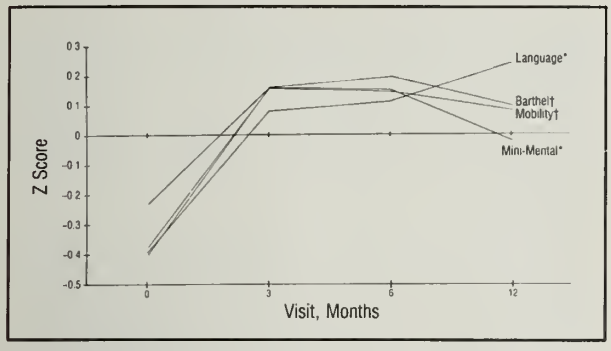

Figure 3.—The time course of improvement in functional deficits of patients following stroke is shown. Four tests were used to measure the amount of improvement from the acute period to 3 months (from Kelly-Hayes et al[3]). * = $P < .01$, † = $P < .05$

restriction of independence to avoid their harming themselves and others. Using medication to reduce hostile and impulsive behavior should be avoided because the usual agents tend to impair orientation and behavior. Reentry programs that teach head injury patients social skills and appropriate behavior for daily living are often necessary for those with cognitive impairment. Some patients become such difficult management problems that they cannot live at home. Improved emergency care for head injury victims is increasing the number of survivors and the need for extensive neurorehabilitation programs and long-term care. This is in part balanced by a decline in the incidence of severe head injury, due to the use of seat belts and airbags in automobiles.

Spinal Cord Injury

Spinal cord injury is a serious problem because of the degree of disability it can cause. It occurs predominantly in two age groups: patients older than 50 years who have cervical osteoarthritis and spondylosis; and young men aged 15 to 25, following automobile or sporting accidents or violence. Survivors, especially those with cervical spinal cord injury, are usually seriously disabled and need expensive and continuous support. The rehabilitation of patients with spinal cord injury is dictated by the physiologic deficits that occur following spinal cord damage or transection.[12-15]

For persons with paraplegia, the problems are compounded by a loss of control over bowel and bladder function and a loss of sensory perception below the lesion level. Rehabilitation programs for those with paraplegia are designed to condition the responses that trigger bladder voiding reflexes by external abdominal pressure or other means, so that patients can predictably empty their bladders. Conditioning bowel function by suppositories and a regular pattern of bowel activity usually assures that the person is not incontinent. Patients are taught to protect areas of anesthetic skin to avoid the difficult problem of decubitus ulcers. Spasticity initially may be a problem for patients with paraplegia and is managed by physical therapy and medication. Later, spasticity usually becomes less of a problem. Programs to increase strength in the upper extremities are necessary for patients to be able to transfer from wheelchairs to automobiles and to move easily and efficiently in wheelchairs. Although patients with paraplegia can be braced so that they can walk and take some steps, they usually find that mobility in a wheelchair is more efficient than trying to manage with braces and canes.

For quadriplegic patients with cervical spinal cord damage, problems are much more complex and difficult. Patients are disconnected from supersegmental control of a number of important functions, such as autonomic nervous system controls and body heat loss and conservation, and are seriously disabled by a substantial loss of voluntary motor function. The lower the cervical spinal cord injury, the more functional the patient can become. Patients who are injured at C5-6 or C6-7 generally have remaining upper arm function that can be enhanced by exercises. High cervical lesions usually leave a patient totally dependent on others. Patients also need training and conditioning in bladder and bowel function so that bladder and bowel emptying can be predictably carried out without the risk of incontinence and so that bladder emptying can be adequate to prevent urinary tract infection. Avoiding excessive high and low environmental temperatures is important because the body has lost its connection with the brain mechanism that senses body temperature changes so that sweating and shivering do not occur below the level of the lesion. Such patients often find it extremely uncomfortable to be outside in warm weather and find it extremely difficult to lose the sensation of being cold when exposed to cold weather.

Perhaps the most difficult problem in persons with cervical spinal cord injury is hyperactivity of the autonomic nervous system. Noxious stimulation below the level of the spinal cord lesion is likely to set off excessive autonomic activity, with elevations of blood pressure, sweating of the head, headache, and a reduced heart rate. This can become dangerous because the blood pressure can rise so high that intracerebral hemorrhage may occur. The most common causes of this abnormal reflex response are a distended bladder or rectum or unrecognized sources of noxious stimulation such as infected toenails or bedsores. Prompt attention to these sources of noxious stimulation usually deals with the problem adequately, although pharmacologic means of lowering the blood pressure may be necessary. Orthostatic hypotension is common in patients with cervical spinal cord injury. Its presence complicates and delays the assumption of the sitting position. Patients usually adapt gradually with sustained acceptable blood pressure while sitting.

The psychological effects of spinal cord injury, especially in the young, revolve around the loss of the capacity to be active, although many patients with paraplegia and quadriplegia do surprisingly well with the aid of modern electronic technology in dealing with their environment and being able to be employed. Sexual dysfunction is a considerable problem, and counseling on this issue is needed as patients begin to realize that the impairments they have after injury may be permanent.

Spinal cord damage also occurs in older persons with

hypertrophic osteoarthritis in the cervical and thoracic spine. They may injure their spinal cord by falling or by gradual pressure on the spinal cord. Surgical management with enlargement of the space available for the spinal cord and nerve roots can be effective in dealing with the problem. Rehabilitation programs are based on the amount of impaired function and are similar to those for younger victims.

Multiple Sclerosis

Neurorehabilitation for persons with multiple sclerosis is becoming increasingly important because of evidence that improvement can occur with carefully monitored exercise and physical therapy. It has also become evident that a neurorehabilitation service is the most suitable place for hospitalization when patients become ill with the common complications associated with multiple sclerosis, such as spasticity, urinary tract infections, decubiti, and exacerbated disease.[16] Patients with multiple sclerosis then do not have the complications of decreased physical activity while they are in an acute care hospital and decreased mobility at discharge. In acute care hospitals, patients are rarely adequately mobilized during hospital stays and often have prolonged periods of bed rest or inactivity.

The common reason for admission of patients with multiple sclerosis to rehabilitation facilities is evidence of spinal cord damage producing partial or complete paraplegia and sometimes quadriplegia. Programs for these patients are similar to those for patients with traumatic spinal cord injury. Disease progression makes rehabilitation results difficult to evaluate, but keeping patients with multiple sclerosis physically active and improving remaining strength allow many patients to remain independent in self-care and often in employment. Inpatient rehabilitation programs for patients with multiple sclerosis are often extremely effective in improving function, but it is difficult to guarantee that improvement produced by a rehabilitation program will be sustained.

Parkinson's Disease

Rehabilitation programs for patients with Parkinson's disease are again becoming more important after being nearly abandoned with the advent of levodopa and dopamine agonist treatment. Before these agents were available, virtually all patients with Parkinson's disease were involved in rehabilitation and exercise programs. It is now evident that this kind of care should be an integral part of the management of these patients.

Patients with Parkinson's disease often benefit from brief periods of inpatient rehabilitation.[17,18] The tendency for a person with Parkinson's disease is generally to become less physically active and to spend large amounts of time sitting. It then becomes difficult to determine reasons for excessive fatigue or an inability to perform self-care activities, and the question arises as to whether this is because of the progression of the disease or to general deconditioning. Placing inpatients on programs of fairly vigorous regular exercise has improved function in many. The distance patients can walk increases, and their need for assistance in daily activities is reduced. These results occur without notable changes in medication. The effects of rehabilitation programs tend to last only six to nine months. The reason for this is not disease progression, but, rather, that when patients return to their home environment, they lapse into their previous habits of inactivity.

Patients with extensive peripheral neuropathy, such as that which occurs following the Guillain-Barré syndrome, are frequently admitted to rehabilitation hospitals because of serious disability. Recovery over several months is common for these patients, and during their period of recovery, it is extremely important to improve their tolerance for physical activity and to avoid the complications that are related to immobility, such as pressure sores, thrombophlebitis, and pulmonary embolus. These persons often benefit from careful orthotic evaluation and the construction of braces to take care of foot and wrist drop while they are recovering. Pain is often a problem, with hyperalgesia and hyperesthesia in parts where peripheral nerve regrowth is taking place; it generally can be managed with analgesics and antidepressants.

The Future of Neurorehabilitation

A number of attempts have been made to apply the data from experiments with animals that suggest that recovery can be augmented and speeded by pharmacologic means and that certain commonly used medications can impede the recovery process. Amphetamine and yohimbine have been found to enhance recovery in rats and cats that have an experimental lesion that produces hemiparesis.[19,20] Agents that retard recovery include phenytoin, haloperidol, clonidine, diazepam, and prazosin.[21,22] Studies in patients with stroke on the effect of amphetamine on recovery and enhancement of the rehabilitation process have not produced convincing evidence of benefit. The potential of using pharmacologic enhancement of recovery is now being extensively investigated as is the potential of clinically used agents to retard recovery.

Promise of a cure of the conditions that bring patients to rehabilitation hospitals is suggested by current laboratory research, but the prospect for the immediate future is limited. In the interval, professionals who have a special interest in the function of the central nervous system should apply their thinking and the scientific method to the evaluation of the problem of rehabilitation to find out what is best to do and how best to do it.

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Role of Neurologists in the Pharmaceutical Industry

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Important advances in the field of clinical neuropharmacology have created an increasing demand by the pharmaceutical industry for neurologists. As recently as a decade ago, neurologists were relatively rare in the pharmaceutical industry. I describe the roles played by industrial neurologists and review both the opportunities and risks of this career path.

(Peroutka SJ: Role of neurologists in the pharmaceutical industry, *In* Neurology—From Basics to Bedside [Special Issue]. West J Med 1994; 161:328-330)

The role of neurologists in the pharmaceutical industry has expanded considerably during the past decade. The primary reason for this change is that novel therapeutic agents are being developed that are likely to revolutionize the clinical practice of neurology. These new therapeutic agents, many coming from the biotechnologic advances in molecular biology and genetics, represent neuropharmacologic progress that was impossible to predict a decade ago. A second notable change that has occurred is that most new pharmaceutical neurologists are entering industry directly from academia. In the past, most entry-level pharmaceutical physicians came from private practice. The lure of breakthrough therapeutics is a likely explanation for the change.

The expanding pharmaceutical need for clinician-scientists with neurologic expertise, however, has not been appreciated by most practicing and academic neurologists. Many lack knowledge about the actual roles filled by pharmaceutical physicians—Spilker and Cuatrecasas provide an excellent detailed overview.[1] In this article I review the activities of pharmaceutical neurologists and discuss both the opportunities and risks of this career path.

Role of Neurologists in Pharmaceutical Companies

The question most frequently asked of an industry neurologist by other neurologists is probably, "What exactly do you do all day?" The day-to-day activities can be divided into three major categories: preclinical, clinical, and business-related functions. Although each component is distinct and can vary among corporations in the amount of time spent in each type of activity, industrial neurologists are likely to participate in all three activities to at least some degree.

Preclinical Development Activities

The majority of research personnel in most pharmaceutical companies is engaged in preclinical activities. A neurologist is often part of a "project team" whose goal is to determine the feasibility of a specific therapeutic concept. For example, many pharmaceutical companies are interested in Alzheimer's disease. Preclinical scientists may seek advice from a team's neurologist on whether a certain animal model may be the best available model of Alzheimer's disease or age-related memory impairment. The neurologist needs to keep the preclinical scientists informed of the relative ease or difficulty of possible clinical trials in Alzheimer's disease. The ability to perform cost-effective therapeutic trials with clearly delineated clinical end points may substantially affect management support of the preclinical project.

Ideally the neurologist and preclinical neuroscience group interact closely. In general, less than 10% of preclinical research projects lead to human therapeutic trials. Therefore, the clinician should be actively participating at the earliest stages of a preclinical project. At this early stage, the role of the neurologist is to assess the scientific, clinical, and business logic of the program. Does the scientific hypothesis make sense from a clinical perspective? Is the potential therapeutic product likely to serve an important clinical need? These are key questions that must be answered for every preclinical research project. Neurologists are uniquely able to provide efficient and in-depth answers to these questions.

If a project progresses to the point that clinical trials are considered, the neurologist prepares an outline of the design of the clinical development plan. This "strategic plan" is then presented to the company management committee that oversees all of the drug development plans. Because of the large expense involved with clinical trials,

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the strategic plan needs to be carefully detailed and supported strongly by preclinical data. Pharmaceutical neurologists often rely on clinical consultants at this stage to assist in the development plan. These consultants are usually academic experts in the field of interest. The experience of the consultants and their enthusiasm for the project can have a beneficial effect on the drug development program.

Clinical Development Activities

After the clinical development plan is prepared, it is presented to Food and Drug Administration (FDA) officials for comments at a "pre-IND" [Investigational New Drug] meeting. The neurologist, preclinical scientists, and academic collaborators often attend the meeting. The FDA officials add their unique perspective to the plan, and their comments and suggestions are important to the long-term success of the project. The immediate assessment to be made is whether the Phase I safety study plans are adequate to ensure that all possible biologic or side effects of the drug can be detected, documented, and analyzed.

Once the Phase I safety studies are completed and the data analyzed, then Phase II studies begin. The goal of the Phase II research is to continue to gather safety data while beginning to look for evidence of drug effectiveness. The neurologist also assists with or directs the identification of appropriate clinical investigators who are often, but not exclusively, persons from academia. The neurologist is a key member of the group that designs and implements these critical studies. The neurologist also "monitors" ongoing clinical trials by evaluating all reported side effects and ensuring that the investigators comply strictly with the protocol.

The clinical team within the company working on the trials often includes several clinical research assistants. Clinical research assistants usually have a nursing background and monitor the clinical trials. Statisticians are also important team members because they are primarily responsible for data analysis. The project team also includes persons from the company's regulatory affairs department who maintain contact with the FDA officials throughout the clinical development process.

The next major development decision occurs at the end of the Phase II trials. The assessment of the Phase II data becomes the major determinant of whether drug development should continue. The neurologist plays a key role in the assessment of the Phase II data. If the decision is to continue into Phase III, then an "end of Phase II meeting" is held with FDA officials to review the available data and the specific clinical design plans for the Phase III trials. In general, at least two large-scale Phase III efficacy trials are required by the FDA for a drug to be approved. These trials are both the most critical and expensive part of the entire drug development project. Once again, the neurologist plays a major role in trial design, investigator selection, and trial monitoring.

Business-Related Activities

At each step in the development process, the pharmaceutical neurologist needs to be aware of the influence that purely business-related factors have on the development program. For example, drugs that treat rare and nonfatal diseases may be difficult to develop because of the enormous expenses required to obtain drug approval. At present, it has been estimated that about $200 million is needed to bring a drug to market. This cost must be balanced by the sales potential of the product. Thus, a possibly excellent therapeutic agent for a rare neurologic disease may never get developed because the sales of the drug would not be profitable for the company. The discontinuation of a project for purely business reasons can obviously lead to substantial frustration for advocates of certain drugs.

A pharmaceutical neurologist is also likely to become involved in business-related issues. The neurologist may be asked to comment on the value of specific therapeutic approaches that smaller companies are frequently trying to license to larger companies. On the other hand, a neurologist in a small company may spend a great deal of time and effort trying to convince larger companies to collaborate on a specific project.

Pharmaceutical neurologists often interact extensively with marketing departments. Marketing expertise is needed initially to assess the size of the potential market for a therapeutic candidate. As the drug nears approval, marketing activity increases. Even after a drug is approved by the FDA, the clinician is needed to interact with the marketing group to assess possible Phase IV clinical trials. These Phase IV trials are usually aimed at identifying possible new indications for marketed drugs.

Clearly, most neurologists are poorly prepared for any type of business-related activities involving drug development. Therefore, most companies provide "management training" sessions for their physicians. No academic analogue exists for the type of management training provided, but the training can be extremely important for developing higher level management skills in a clinician.

Opportunities in Industry

Teamwork

Although difficult to quantify, the most important opportunity in industry for a neurologist is the power of teamwork. A neurologist is likely to interact daily with outstanding preclinical scientists, clinical trial experts, regulatory affairs officials, and marketing experts. A unique opportunity exists to interact with intelligent and motivated people with a wide variety of skills. Successful industrial neurologists enjoy this type of interaction, and it is crucial to the success of any given project.

Interaction With Leading Academic Experts

A neurologist is likely to initiate and develop relationships with the academic experts in a given field. For breakthrough therapeutic products, the possible "academic" rewards of successful clinical research can be substantial. The neurologist is usually encouraged to attend and participate in conferences related to specific projects. An

ongoing awareness of the preclinical and clinical advances within any specific therapeutic area is essential to all development projects.

Financial Remuneration

It is commonly assumed that industrial neurologists are compensated well financially. In reality, salaries average about 20% higher than equivalent academic positions. But industrial neurologists may also receive stock options and bonuses that could increase total remuneration considerably. In general, industrial neurologists probably earn more than most academic neurologists but less than many physicians in private practice.

Lifestyle

The most striking difference between the life of an industrial neurologist and other neurologists is the lack of essential clinical responsibilities. In general, no night call is required, although unexpected adverse events may occur at any time during clinical trials. In addition, most corporations allow their clinicians to have a half day per week of clinical time. This usually occurs at a nearby academic center. In general, industrial neurologists probably work on average 40 to 60 hours per week in the office and, in addition, travel about 10% to 25% of the time.

Risks for Neurologists in Industry

Loss of Personal Independence

Although the concept of "teamwork" appeals to many people, it also means that a person may lose much of the sense of "being one's own boss." The perceived value of "independence" is highly subjective, however, and for many persons may not be an issue. On the other hand, industry is unique in that nearly all physicians are essentially under the direction of nonphysicians. Being directed by nonphysicians (usually businesspeople) is often difficult for physicians, given the fact that such people are rare in medical school and house-staff training programs. In addition, marketing departments may have a major influence on clinical projects, which is difficult for a neurologist to appreciate. For example, the "small size of the market" may be cited as a reason to discontinue a research program despite the fact that an effective agent may have been found for a rare medical condition.

Clinical Skills Not Appreciated

A more general problem is that medical training focuses on developing individual skills. These skills may sometimes not receive their appropriate recognition from persons with little medical training or knowledge. Clearly a lack of appreciation of the clinical value of a neurologist can be a major drawback of industrial settings.

Clinical Skills Fade

Clinical skills inevitably decline as a neurologist decreases clinical activities. This change need not be sizable and is certainly not irreversible, but it is unavoidable. Maintaining a half day per week of clinical activity is probably the best way to reduce this risk.

Intellectual Conflict of Interest

The most serious professional risk for a person is the possible intellectual conflicts of interest that may occur. To be successful, the neurologist must believe that a project being developed will be useful. This belief must be constantly balanced by an objective analysis of the data. The desire to obtain "good data" may be based on personal, intellectual, or financial goals. Neurologists in industry, like many academic neurologists, must maintain an objectivity that can be difficult when substantial pressures exist to succeed.

Summary

Neurologists in the pharmaceutical industry are playing an increasingly important role in the development of neuropharmacologic advances. Industry offers the opportunity to perform breakthrough clinical research in a setting that rewards teamwork. The pressure to succeed, however, can be more immediate than in academia and can often lead to unique frustrations. On balance, life in the pharmaceutical industry can be both rewarding and challenging for a neurologist interested in advancing the field of neuropharmacology.

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Future Role of Neurologists

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Clinical neurologists in the health care system of the future should have a multifaceted role. Advances in the basic understanding of the nervous system and therapeutics of neurologic disease have created, for the first time in human history, an ethical imperative to correctly diagnose neurologic disease. In many situations, the neurologist may function as a consultant and principal physician for patients with primary nervous system disorders including Parkinson's disease, multiple sclerosis, Alzheimer's disease, epilepsy, migraine, cerebrovascular disease, movement disorders, and neuromuscular disease. Other important roles for neurologists include the training of future physicians, both neurologists and primary care physicians, the application of cost-effective approaches to care, and the support of health care delivery research and academic programs that link basic research efforts to the development of new therapy. To be successful, future residency training programs should include joint certification opportunities in both neurology and general medicine, and training programs for clinical investigators should be expanded. Despite its threats to specialists, managed care should also provide opportunities for new alliances among neurologists, other specialists, and primary care physicians that will both improve patient care and increase efficiency and cost-effectiveness.

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Diseases of the nervous system occupy a prominent place among medical illnesses in terms of their frequency and the emotional burden they place on patients and their families. The enormous financial cost of neurologic diseases—estimated in 1992 at more than $400 billion in the United States—reflects the profound effect these disorders have on society.[1] With the aging of the population and the increasing longevity of persons with cancer, heart disease, and other disorders, the number of patients with neurologic disease will further increase in coming years.[2] New and effective treatments, available now or in the near future, will add additional pressure on the medical community to diagnose and treat neurologic diseases efficiently.

The neurologic method, consisting of diagnosis by careful neuroanatomic localization of symptoms and signs, is most effectively applied by experienced practitioners. Skillful application of the method requires, for all but the few most capable, frequent repetition. The blind application of neuroimaging and other diagnostic testing methods will not compensate for deficient skills in clinical neurologic assessment and will add substantially to the cost of care. As a result, it is not surprising that many physicians are uncomfortable in evaluating neurologic problems.

These considerations might translate into self-confidence among neurologists and optimism over the future of the specialty.[3] There should be a growing demand for neurologists, who currently represent only 1.5% of all physicians and whose clinical ranks are reduced by 10% of neurologists, compared with 3% of physicians at large, who are primarily or exclusively engaged in biomedical research.[1] And yet, some well-intentioned assessments of health care needs tell us that there is a gross oversupply of neurologists and that we need to reduce their numbers dramatically, perhaps by twofold to threefold.[4,5] Some successful managed care programs employ a few neurologists who serve limited and clearly defined roles in their systems. Canada is currently training six neurologists a year nationwide, a tenth per capita of the number accepted each year in US training programs. Regardless of which supply estimates are correct, a fundamental change in the nature of patient care provided by neurologists is likely to occur. One cannot assume, without proper planning, that these changes will necessarily result in improved or more effective patient care. Any conclusions regarding the need for neurologists are dependent on the assumptions used to define the future role for neurologists within the health care system.

Societal Needs and Public Policy

Public policy aimed at reducing the number of specialists in clinical medicine is being driven by concerns over the cost and accessibility of medical care. Neurology will be affected by the anticipated reduction in the number of specialists and must evolve within the new health care environment.[6-8]

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The future role of specialists will be determined by the broad needs of patients and society.[9,10] Patients' needs include improving clinical results by reducing mortality and increasing the quality of patients' lives.[11] The needs of society include reducing the cost of medical care and developing improved methods for preventing and treating disease. These goals will require a commitment of resources for four purposes:

- Cost-effective methods of health care delivery must be developed and implemented;
- Residents in neurology and in primary care must be trained to apply cost-effective approaches to the use of diagnostic technology and therapy;
- Academic programs must support and train physician investigators expert in designing and implementing clinical research relevant to health care delivery; and
- Comprehensive academic programs that link basic research efforts to the clinical care of patients must be protected to foster the continued application of new knowledge to the development of cost-effective prevention and therapy.[12]

Our discussion of the future role for neurologists incorporates these considerations and addresses several questions: Should neurologists function exclusively as consultants? Is there a role for neurologists as providers of primary or principal care? What type of neurologic training should be available to primary care residents and physicians in practice? Are outcome data available to support an increased use of neurologists in the health care system? How many neurologists are needed to deliver quality health care? The answer to the last question depends on many factors, including a description of the range of tasks done by neurologists and evidence that neurologists make a difference in the diagnosis and management of neurologic disease.

Neurologist-Consultants

The traditional role of neurologists has been to provide consultative clinical services to patients and referring physicians. Three developments have changed this traditional role. First, dramatic advances in our understanding of the pathogenesis of many common neurologic diseases have been coupled with the development of new (and expensive) diagnostic methods. Second, therapies for neurologic disorders such as epilepsy, stroke, multiple sclerosis, headache and other chronic pain syndromes, Parkinson's disease, and neuromuscular disorders have increased in number and effectiveness. These two developments have created, as never before, an ethical imperative to correctly diagnose neurologic diseases. Third, the emergence of neurology as an independent specialty that treats patients with neurologic problems has isolated primary care residency trainees from adequate exposure to neurologic problems. These developments have resulted in a greater role for clinical neurologists and a reduced role for primary care physicians in the care of patients with neurologic disease.

Neurologic care is neither primary care nor solely specialty care. Neurologists currently function as the principal physician for many patients with long-term neurologic illness. Principal care refers to patient care provided by a specialist for a patient's principal medical illness or set of related problems.[13] Principal care is not primary care. Examples of neurologic disorders for which neurologists may provide principal care are Parkinson's disease, multiple sclerosis, Alzheimer's disease, epilepsy, migraine, cerebrovascular disease, movement disorders, and neuromuscular disease. The role of the neurologist as a principal care provider does not diminish the role of the primary care provider. The role of the physician who provides a patient's primary care does not diminish the role of the neurologist. In fact, there is a great need for primary care physicians and neurologists to work together, both in the care of patients and the education of future physicians.

Neurologic Training for Primary Care Physicians

As of this writing, many managed care systems have assigned substantial clinical responsibility for the care of neurologic patients to primary care physicians. How might neurologic instruction of generalists-in-training or practicing primary care physicians be accomplished?[14] The five components needed to establish an effective training program are faculty, primary care residents, an ambulatory care training facility, resource support for a new educational program, and a commitment to investigating the cost-effectiveness of diagnostic and therapeutic interventions.

There will be a central role in the future for physicians dually trained in primary care and neurology to teach and provide patient care and to serve as role models for neurology and primary care residents.[15] These specialists, trained in internal medicine or pediatrics as well as neurology, will function comfortably as both consultants and principal physicians. Some of these physicians will also be trained in modern methods of epidemiology, biostatistics, public health, or clinical trials design. Such physicians are currently in short supply and high demand. Many have trained in a haphazard or inefficient way, in contrast to the well-organized training programs that characterize the education of most laboratory-based physician-scientists. Comprehensive training programs specifically designed to provide these skills must be developed, improved, or expanded in size. These clinical investigators, equipped with modern tools for clinical research, will be uniquely positioned to obtain grant support and to lead academic clinical programs. They will be among the most valuable assets of a competitive program, and this career path should prove to be increasingly attractive to future generations of academicians.

Expanding joint certification programs in neurology and a primary care specialty will help to encourage this career path. Joint certification already exists for pediatrics and child neurology and could be formalized also for internal medicine and adult neurology. Joint certification programs can provide medical students and residents with

important role models that foster effective teamwork between primary care and neurology physicians. The greatest challenges to implementing these proposed changes are the financial costs of implementation and the barriers that have traditionally segregated patients by diagnosis and along hospital departmental lines.

Outcome Data and the Role of Neurologists

There are specific circumstances in which the use of neurologists positively affects the outcome of neurologic therapy or the cost-effective use of diagnostic technology. Although mortality end points provide the most specific measures of therapeutic success or failure, neurologic diseases frequently result in long-term disability and lowered quality of life rather than death. The quality of life can be difficult to measure, but specific interventions that rely on the unusual skills of a clinical program or a person can be measured and expressed as a therapeutic or diagnostic outcome.

The beneficial results of a surgical procedure to alleviate the seizures of a patient with intractable epilepsy provide evidence of the effectiveness of clinical programs made up of neurologists.[16-18] The most successful epilepsy surgery programs carefully select the patients most likely to benefit from surgical intervention based on features such as evidence of previous maximal medical therapy, localization of a seizure focus, the extent to which seizures impair the lifestyle of a patient, a pathologic substrate for seizures, and the likelihood of postoperative complications. Approximately 50% to 70% of properly selected patients with temporal lobe epilepsy are free of seizures after the surgical procedure. The resulting economic and medical care savings over the lifetime of a patient are likely to be substantial. Outcome data for different epilepsy surgery programs can be compared to determine which centers might be designated as "centers of excellence" in a new health care system. Outcome data are also available to support the benefits of specialized stroke units and intensive neurorehabilitation.[19-25]

A similar analysis can be used to evaluate the cost-effective application of neuroimaging.[26,27] For example, the cost of a magnetic resonance imaging (MRI) scan of the brain is about six times the cost of an initial history and examination by a neurologist. The number of neuroimaging procedures ordered by primary care physicians is increasing rapidly. Some studies suggest that primary care physicians may not order neuroimaging studies in a cost-effective manner. If the use of brain MRI can be reduced by one of every five scan requests, then a screening neurologic history and physical examination will be cost effective. Reducing the number of MRI scans could probably be achieved with little or no adverse effect on public health.

Any algorithm or practice guideline for the diagnostic evaluation of a neurologic symptom or sign will assume that a competent neurologic history and examination have been done. In a practical sense, "gatekeeping" for neuroimaging procedures should rest exclusively in the hands of physicians who possess these clinical skills. In addition to neuroimaging, many other important questions regarding the appropriate use of diagnostic technology applied to patients with neurologic disorders are worthy of investigation.

These guidelines and measures may be of secondary importance for some. Neurologists must work with consumer groups to foster the development of clinical practice guidelines that balance quality of care with cost of care. In a survey from 102 managed care organizations, six factors were ranked for their importance to the success of managed care (R. Winslow, "In Health Care, Low Cost Beats High Quality," *The Wall Street Journal*, January 18, 1994, p 1B). The percentage of managed care organizations that ranked each factor either first or second in importance were as follows: price, 69%; patient satisfaction, 50%; access to physicians, 31%; quality improvement processes, 20%; national network affiliation, 11%; use of clinical practice guidelines, 10%; and publishing results, 9%. Clinical practice guidelines and publication of outcome measures were perceived as less important factors influencing the success of managed care. A strong voice for quality-of-care standards as measured by patient outcomes and standardized by clinical practice guidelines needs to be encouraged among consumer groups and health care professionals.[28]

How Many Neurologists Are Needed?

Considerable disagreement exists about the number of neurologists required to serve the needs of society and patients. The source of disagreement is buried among the assumptions used to project neurologic personnel needs. For example, early reports suggesting that the supply of neurologists was outstripping need were based on several assumptions. First, the dramatic growth rate in the number of neurology residents during the 1970s was expected to continue. In fact, the number of neurologists completing residency training annually reached a plateau in the late 1970s.[29] Primary care residents were expected to receive more clinical neurology training in the future. Menken predicted in 1981, "As more primary care physicians graduate from programs with greater emphasis on diagnosis and treatment of neurologic illness, the total demand for neurologic consultations will be less."[4(p2402)] He clearly recognized the requirement that primary care physicians develop adequate skills in neurologic assessment to decrease the demand for neurologic consultants. During the past decade, however, the formal neurologic training of primary care physicians appears to have decreased rather than increased. It thus appears that the education of primary care physicians may conflict with assumptions of managed care and threaten the level of care for patients with neurologic disease.

An accurate projection of neurology personnel needs has been limited also by the failure to recognize the effect of the growing number of older Americans.[2] The number of adults older than 85 years will approximately double from 1980 to 2020. Currently, 15% of men and 25% of women older than 85 years require nursing home place-

ment because of illness and disability. The prevalence of dementia reaches 28% at age 85 years and older. The demand of these senior citizens for neurologic services in the future will be considerable.

Recent estimates of the need for neurologists have ranged from a low of 5,000 to a high of 16,000.[5-7] The current "supply" is about 13,000. The disparity between high and low estimates of need reflects multiple uncertainties. The future role of the neurologist is not defined clearly. The number of neurologists per capita differs by about a factor of 10 in different regions of the United States, from a low of 1 per 100,000 in Wyoming to a high of 11 per 100,000 in the District of Columbia.[7] These dramatic differences suggest that neurologists may be used in various ways, depending on supply. There are little data assessing how neurologists currently spend their time. For example, board-certified active and retired neurologists are included in the same estimates of future need. Furthermore, time spent in academic activities or those not involving patient care is not assessed. It is not clear to what extent accurate projections of neurologic personnel needs can be made from the incidence of neurologic diseases alone. For example, a careful evaluation by neurologists of symptoms that do not ultimately reflect structural neurologic disease (for example, chronic fatigue or pain) is extremely helpful to patients and primary care physicians. These patients are not included in need projections if the projections are to be based solely on the known incidence of neurologic disease. Reliable projections will also depend on two additional unknown variables: the number of neurology residents who will be trained in the future, and the adequacy of neurologic training for primary care physicians.

It would be unfortunate if the role of neurologists in a new health care system were to be confined to consultation services only. The unique skills of neurologists place them in a useful position to provide emergency or continuing care of patients with neurologic diseases. Examples of the former include stroke and other acute neurologic catastrophes that require intensive in-hospital care. Examples of the latter include the participation of neurologists in team settings for the care of patients with chronic nervous system diseases including Alzheimer's disease, multiple sclerosis, Parkinson's disease, epilepsy, pain, and neuromuscular disorders. A rapid growth in the number of effective therapies for these disorders will further increase the appropriate role of neurologists in neurorehabilitation and other long-term-care settings. To thrive, the specialty will need to demonstrate the effects of its services on outcome and cost and to work effectively with primary care physicians in the managed care arena.

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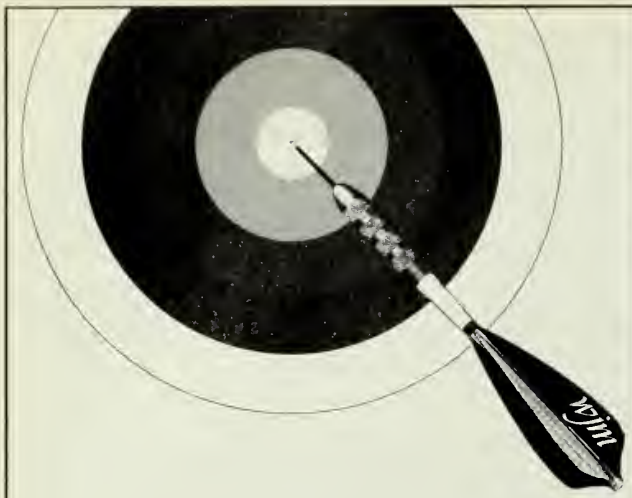

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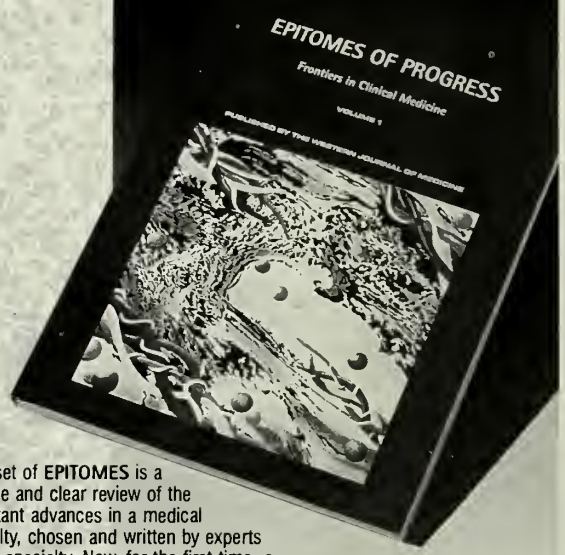

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LUSH HAWAII needs Internists, Pediatricians, Family Practitioners, OB/GYN $160K, Orthopedists $200K. Multispecialists. San Diego Occupational Medicine, $150K or OB/GYN. Loan Repay. Clear Speech. CVs: LAM Associates, Dept W, 444 Hobron Ln, #207H, Honolulu, HI 96815-1229. Call Pat Lam, (800) 258-4526, 11-10 pm California time.

SOUTHERN CALIFORNIA. Rural non-profit health clinic needs a General Practitioner who desires: direct primary health care, participation in chart review and quality assurance, clinic hours to only 7:00 pm, minimum hospital admissions, hospital on call two weekends per month, excellent benefits, malpractice 100% paid. Please send CV to: Clinicas de Salud del Pueblo, Inc., Personnel Office, 1116 "K" St, Brawley, CA 92227.

OREGON. FAMILY PRACTICE clinician teachers needed for Oregon Health Sciences University Department of Family Medicine. We seek clinician teachers for new neighborhood practices. Duties are chiefly patient care plus some resident and student teaching. Obstetrics and hospital care of patients desired. Send CV and three references to L.J. Fagnan, MD, Dept of Family Medicine, OHSU, Mail Code FP Portland, OR 97201-3098. AA/EO Employer.

FAX YOUR AD to (415) 882-3379. Or call us for more information at (415) 882-3376.

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SPOKANE, WA 99207
(509) 482-2164
FAX: (509) 482-2456

OREGON. Medical Director needed for Oregon Health Sciences University Department of Family Medicine. Duties are to provide patient care and resident and student teaching at the Family Practice patient care clinic. Obstetrics and hospital care of patients desired. Send CV and three references to L.J. Fagnan, MD, Dept of Family Medicine, OHSU, Mail Code FP, Portland OR 97201-3098. AA/EO Employer.

FAMILY PRACTITIONERS. Immediate locum tenens and permanent assignments for Family Practitioners who do Obstetrics. Ongoing needs in numerous states. We compensate. We insure. Call Frank Canaday today toll-free at (800) 226-6347 for details. "HKA...Placing tomorrow's healthcare needs today."

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OREGON/WASHINGTON. BC FAMILY PRACTITIONERS to join established groups in Portland and Seattle. Balanced lifestyle near water and mountains, four seasons, clean air. Country or city locations offer abundant cultural and recreational activities. Light call, generous guarantee, benefits, partnership. OB optional. Call Jan, (800) 789-1190 or (206) 389-9191.

(Continued on Page 341)

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PHYSICIANS WANTED

REWARDING OPPORTUNITY to practice the full range of Family Medicine (with Obstetrical option if desired) in a long-standing community health center. BC/BE Family Practitioners needed to join existing staff composed of Family Physicians, Internists, and Pediatricians on the Waianae Coast. Academic positions also available. Full benefits package and competitive salary. If interested, call or send CV to Darlene Hoffmaster, Waianae Coast Comprehensive Health Center, 86-260 Farrington Highway, Waianae, HI 96792; (808) 696-1442.

CALIFORNIA. MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Medicine or Family Practice specialists preferred. Contact Sylvia Amendola, Personnel Director, Doctors on Duty Medical Clinics, 223 Mount Herman Rd, Scotts Valley, CA 95066; (408) 438-9341.

ENJOY THE GREAT SOUTHWEST. Thomas-Davis Medical Centers, one of Arizona's fastest growing multispecialty groups is seeking BC/BE Internal Medicine, OB/GYN, and Hematology/Oncology Physicians. 200 physicians strong, TDMC has provided health care services in Arizona for more than 75 years. For more information regarding this practice opportunity, contact William Trainor, TDMC, 6135 N 7th St, Phoenix, AZ 85014, or call (800) 539-2529, or FAX CV to (602) 530-6255.

PACIFIC NORTHWEST AND ROCKY MOUNTAIN/ SOUTHWEST LOCATIONS. Locum tenens assignments in Emergency Medicine, Primary Care, and Radiology. Urgent need for locum tenens. Benefits include malpractice, lodging, and transportation. Assignments vary in duration. Permanent placement also available. Call or write Lorie or Susan, Interim Physicians, 4155 E Jewell, #1018, Denver, CO 80222; (800) 669-0718.

BC/BE FAMILY PRACTITIONER with interest in OB and a commitment to caring for the underserved needed to join clinics in Grandview and Walla Walla, Washington, and Hermiston, Oregon. All clinics located in rural settings with abundant recreational activities. Competitive salary, Public Health Service loan repayment slots, and excellent benefit package including paid malpractice. Contact Mayling Chin, Recruiting Specialist, or Ann Garza, Director of Personnel at Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948, or (509) 865-5898.

CALIFORNIA, ACADEMIC, MULTISPECIALTY group practice seeks Family Practitioners, Internists, and Pediatricians for Primary Care practice opportunities. These physicians will qualify for faculty appointment in the School of Medicine. They will admit patients to the school's three teaching hospitals. They will refer specialty cases to faculty colleagues. Competitive salaries are being offered with potential for incentive bonus. A comprehensive benefit package is provided. Respond to Loran Hauck, MD, Medical Director, Loma Linda Faculty Medical Group, 11370 Anderson St, Ste 3000, Loma Linda, CA 92354; (909) 799-3315.

CALIFORNIA. Ambulatory Care/Family Practice–CEP is a partnership of Ambulatory Care and Emergency Medicine specialists. We currently staff nine free-standing clinics in northern, central, and southern California, and have upcoming openings for physicians specializing in Family Practice. We offer shared ownership, excellent compensation, health, and disability insurance, retirement program, and many other benefits. For more information, send CV or call John Gravette, CEP, 2101 Webster St, Ste 1050, Oakland, CA 94612; (800) 842-2619.

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(Continued on Page 342)

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(Continued from Page 341)

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Northwest Permanente, P.C., a professional group of physicians providing medical services to 380,000 members of Kaiser Permanente in Oregon and SW Washington, has full-time and part-time opportunities in general family practice or urgent care for BC/BE Family Physicians and Internists in the Portland/Vancouver and Salem, OR areas and Longview, WA. In Salem, opportunities exist for Family Physicians or Internists with a special interest or expertise in geriatrics.

Our program offers a professionally stimulating environment, a quality lifestyle in the Pacific Northwest, signing bonus and a competitive salary/benefits package. **Forward inquiry and C.V. to: W. J. Weiland, M.D., Regional Medical Director, NORTHWEST PERMANENTE, P.C., 2701 N.W. Vaughn St., #300, Portland, OR 97210-5398. EOE.**

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Los Angeles, CA 90067

Or Call: (310) 556-2126, FAX (310) 556-1604

AT NO COST TO PHYSICIAN

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PHYSICIANS WANTED

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OCCUPATIONAL MEDICINE

EXCELLENT OPPORTUNITY. Large multispecialty group with an expanding Division of Occupational Medicine has an immediate opening for a qualified, energetic physician. We are seeking a career-minded physician with superb clinical and communication skills. Experience with managed care, computers, and teaching is desirable.

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Medical Staff Coordinator
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COME TO THE LAND OF ENCHANTMENT. Sunny New Mexico seeking senior physician for 300-bed state-operated facility for people with developmental disabilities. Seeking individual who is looking for a challenge and personal growth, able to provide primary care to adolescents and adults with developmental disabilities, willing to work on a multidisciplinary team, and willing to provide education to University of New Mexico trainees. Potential for academic appointment. Minimum qualifications: graduation from an accredited medical school, completion of an approved internship and licensure by the New Mexico Board of Medical Examiners. For information contact Javier Aceves, MD at (505) 841-5226.

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CALIFORNIA. EXCELLENT OPPORTUNITY available in 1994 to early 1995 for a BC/BE oncologist-hematologist to join a busy, two-person, subspecialty practice in San Francisco bay area. Modern facilities available to deliver high quality, outpatient-based, comprehensive cancer care. Protocol participation available through SWOG-NSABP. Extremely competitive salary and benefit package leading to early partnership. Please send CV to Number 297, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NORTHERN CALIFORNIA RECREATION AREA. Multispecialty group has immediate opening for a Family Practice physician. Clinical activities involve full range of Family Practice outpatient and inpatient practice. Beautiful northern California location offers abundant recreational opportunities as well as small town living. Competitive salary and comprehensive benefit package. Please send CV to 10978 Donner Pass Rd, Truckee, CA 96161.

Experience Colorado!

An outstanding **Family Practice** opportunity awaits you in this friendly Colorado community! Our well-established and successful group is seeking an associate to provide full-range Family Medicine and will provide a competitive *income guarantee*, comprehensive *benefits* and 1-in-4 call coverage to the right candidate.

Best of all, you and your family will benefit from the **fantastic lifestyle** available with access to year-round outdoor recreation as well as the great schools, family-oriented community and low cost of living in the area. Call today for details, **SHANNON FOX, 1-800-235-6745.**

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(800) 945-4066/FAX (509) 484-6317

(Continued on Page 344)

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PHYSICIANS WANTED

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CHAIRMAN Family Medicine/Professor/ Associate Professor, Administrator, clinician, educator to lead the growing Las Vegas programs of the Department of Family and Community Medicine. This exciting program has filled residency and required third-year clerkship in a Department named, "Outstanding Clinical Department" by the classes of 1991-93. Requires administrative and teaching skills and participation in clinical activities including obstetrics. BC Family Physician eligible for licensure in Nevada. Administrative, clinical, and teaching experience required with experience as residency, group practice, or medical director preferred. The School of Medicine is a statewide medical school experiencing exciting growth and development of its Las Vegas Clinical Campus and implementation of new generalist curriculum. Competitive salary and benefits. *AA/EOE. Submit letter of application, CV, and references to:

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Physician, San Diego State University Student Health Services ($6,544-7,920/mo)

Excellent opportunity for PC physician interested in a college health career. SDSU Student Health Services, a nationally recognized, AAAHC accredited clinic located in "America's Finest City" is seeking CA licensed, BC physicians for permanent full-time ten-month positions. Experience with adolescents/young adults preferred. Clinic also involved in research projects and coordinates the UCSD/SDSU Preventive Medicine Residency. Generous benefits package. Send résumé to: Kimberly Johnson, Student Health Services, San Diego State University, 5500 Campanile Dr, San Diego, CA 92182-4701.

SDSU is committed to a diverse workforce and affirmative action and is an EEO employer. SDSU does not discriminate against physically challenged persons.

PHYSICIANS WANTED

The **Prescott VA Medical Center** is seeking **BC/BE Internal Medicine physicians**, one with an interest in **Infectious Disease**, as full-time staff physicians to provide primary care. Prescott, the "mile-high" Old West city is conveniently located 98 miles north of Phoenix, the state capital. At an altitude of 5,300 feet, the city is nestled in the mountainous, ponderosa pine area of north central Arizona. Lots of sun in a dry four-season climate, fresh air, and recreation abound. *Money Magazine* rates **Prescott, Arizona** as the **number one city to live in.** Malpractice is covered. Interested and qualified candidates should send CV to:

Bruce Manziello, MD, FACP
Chief of Staff
VA Medical Center
Attn: (11) Prescott, AZ 86313
or call (602) 776-6009

EOE

INTERNAL MEDICINE/IMMEDIATE CARE, SOUTHERN CALIFORNIA. Dynamic multispecialty medical group well-positioned to meet the future challenges of health care has two outstanding full-time positions available in Internal Medicine and Immediate Care for BC/BE Internal Medicine physician team players. Immediate Care physician must be comfortable with Acute Medicine, Pediatrics, OB/GYN, and Orthopedics. Positions offer secure, balanced professional and personal lifestyle with competitive salary and comprehensive benefit package. HealthCare Partners Medical Group is one of Southern California's leading providers of quality medical care. For further information, please call or submit CV to HealthCare Partners Medical Group, Attn: Jan Webb, Provider Services, 1025 W Olympic Blvd, Los Angeles, CA 90015; (213) 623-3065, ext 3396.

OREGON–PRACTICE MEDICINE IN THE LUSH, GREEN WILLAMETTE VALLEY. Multi-specialty group seeks BC/BE Internist to join department of eight. Excellent salary plus incentive, outstanding benefits. Salem, the state capital, is 40 miles south of Portland, close to ocean, mountains. Great family community. Contact Yvonne Carscadden, Salem Clinic, 2020 Capitol NE, Salem, OR 97303 or call (503) 399-2470.

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CALIFORNIA, OUTPATIENT, NO CALL, FLEXIBLE HOURS. Primary and urgent care: desirable opportunities for BE/BC Family Physicians to join established outpatient practices. Flexible scheduling, no nights and incentive-based compensation in a family practice and urgent care setting. Positions available for Staff Physicians in Clovis and Fresno, Medical Director in Redding. Family-oriented communities, affordable housing, good schools, access to urban amenities, culture, National Parks,and recreation. Contact Ellen Montague, Physician Search Consultant, (by phone, FAX or mail a CV) Fischer-Mangold, PO Box 788, Pleasanton, CA 94566, phone and FAX at (510) 484-1200 and (800) 227-2092 outside California.

PHYSICIANS WANTED

BC/BE PHYSICIAN WITH CALIFORNIA LICENSE to do physical exams for national organization. Part-time flexible hours, $75/hr. Plus travel. Please FAX résumé to (415) 397-4407.

FACULTY POSITION, DIVISION OF METABOLISM, ENDOCRINOLOGY, AND NUTRITION at the University of Washington is recruiting a full-time faculty member at assistant professor level. Closing date for applications: 10/15/94. Requirements: training in general medicine with subspecialty training in Endocrinology, Metabolism, and Diabetes. Candidate needs strong clinical and research background in diabetes with demonstrated ability in collaborative research. Candidate must have demonstrated ability to direct activities of a clinical site for a multi-center prevention trial in type I diabetes. Appointee will serve as Associate Director of a Clinical Research Core within a DERC and will participate in clinical activities at a Diabetes Care Center. Candidate should have grant funds to provide salary support. Send CV to Jerry Palmer, MD, Seattle Veterans Affairs Medical Center, MS-111, 1660 S Columbian Way, Seattle, WA 98108. Women and minorities encouraged to apply. The University of Washington is an Affirmative Action, Equal Opportunity Employer.

PSYCHIATRIST TO ASSUME COMFORTABLE PRACTICE as current psychiatrist retires. Position is in a group practice of community mental health agency and entails direct treatment with clients and supervision of dedicated staff of therapists and case managers. Opportunities to do training and community education. Located in sunny south-central Washington in Tri-Cities riverfront community of 100,000 population. Within a couple of hours drive of hunting, skiing, and other recreation areas. Must be Board Certified or eligible for certification. Please send vita to: Sunderland Family Treatment Services, 8340 Gage Blvd, #205, Kennewick, WA 99336. (509) 736-0704, FAX (509) 783-6986.

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GENERAL SURGEON WITH BROAD SKILLS NEEDED for full-time post in a spectacular SE Alaska town with unlimited recreational opportunities. Call (907) 747-3024 evenings.

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PACIFIC NORTHWEST: WASHINGTON, OREGON, IDAHO. BC/BE physicians needed, Family Practice, Internal Medicine, OB/GYN, Pediatrics, Emergency Medicine Director. Call Eva Page, Page & Associates, Physician Recruiting, (800) 833-3449 or send CV to 1420 NW Gilman Blvd, Ste 2133, Issaquah, WA 98027.

ADS GET RESULTS!

(Continued on Page 345)

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PHYSICIANS WANTED

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THE CALIFORNIA DEPARTMENT OF CORRECTIONS has positions available in one of our newer prison complexes in the WASCO STATE PRISON RECEPTION CENTER. Located near Bakersfield and San Luis Obispo, it offers easy access to the coast and mountains, and affordable housing in open country for great family living. We offer competitive salary and excellent benefits, and A NEW SAFETY RETIREMENT PACKAGE. For more information, call:

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or FAX your résumé to (916) 327-1436. EOE.

PACIFIC NORTHWEST. Placement specialists serving northern California, Oregon, Washington. City or rural, group or solo. Internal Medicine, Family Practice, OB/GYN, General Surgery, Pediatrics, and all other specialties. Barbara Stoefen, President, The O'Kane Group, 25 NW Minnesota Ave, Ste 7, Bend, OR 97701; (800) 451-0700, FAX (503) 389-5134.

SACRAMENTO. BC/BE PHYSICIAN for busy urgent care center. Excellent package with early partnership. Send RV to Number 298, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CALIFORNIA–SAN LUIS OBISPO AREA. Position available in Urgent Care center on the beautiful central California coast. Competitive compensation, malpractice paid. Prefer physicians with experience or residency training in Emergency Medicine or Family Practice. Send CV to Medical Director, 283 Madonna Rd, Ste B, San Luis Obispo, CA 93405

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SOUTHERN CALIFORNIA. BC FAMILY PRACTITIONER, some administrative responsibilities, light call, competitive guarantee, benefits. High desert community. Call Patience Schock, (800) 765-3055, or (314) 725-1892.

PORTLAND, OREGON. BC/BE in group practice. Rapid population growth and an exceptional economic picture make this an ideal environment for successful practices. Excellent compensation, benefits, and call. Affiliated with the Sisters of Providence Catholic Health System. Affirmative action employer. Immediate opportunities and openings for 1995 graduates. Send CV and references to Mark May, Sisters of Providence Health System, 4805 NE Glisan St, Portland, OR 97213; (503) 230-6155, FAX (503) 230-6858.

ORTHOPAEDIST–BC/BE, California licensed, needed for San Francisco based multispecialty medical practice. Primarily forensic medical practice (evaluation and expert witness evaluations in workers' compensation, personal injury, etc). Excellent opportunity for experienced clinician looking to emphasize evaluation and consultation practice as opposed to heavy treatment based practice. Full-time and part-time employment available, exceptionally high income potential, full benefits, and 401K. Submit CV and letter stating professional goals and availability to Administrator, 2040 Polk St, Box 337, San Francisco, CA 94109.

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PHYSICIANS WANTED

SOUTHERN IDAHO URGENT CARE. Expanding Immediate Care with emphasis on quality. Live and work near a variety of outdoor recreation. Located near Yellowstone Park, Sun Valley, Jackson Hole, and the Tetons. This established organization will be opening a new facility. Reply with CV in confidence to PO Box AK, Twin Falls, ID 83303.

SAN FRANCISCO BAY AREA. Physician wanted for growing Occupational Medicine practice, full-time, competitive salary, benefits. Call Dr. Boni at (510) 614-3715.

POSITIONS WANTED

DIAGNOSTIC RADIOLOGIST, ABR CERTIFIED with interventional fellowship desires private practice or clinic practice situation in Montana or Idaho. Please reply to Number 300, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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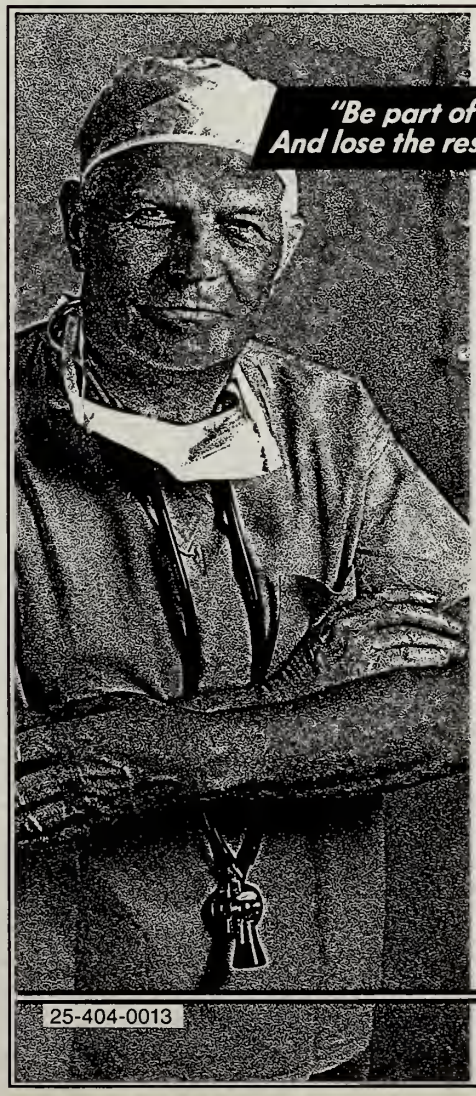

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(Continued from Page 345)

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† Latest available annual data: January to December 1991.

‡ *In vitro* susceptibility does not necessarily imply *in vivo* efficacy.

Please see brief summary of prescribing information for contraindications, warnings, precautions and adverse reactions on adjacent page.

References: 1. Neu HC, Wilson APR, Gruneberg RN: Amoxicillin/clavulanic acid — a review of its efficacy in over 38,500 patients from 1979 to 1992. *J Chemother* 1993;5(2):67-93. **2.** Data on file, SmithKline Beecham Pharmaceuticals. **3.** Data from the Institutes for Microbiology Research, Franklin, Tenn. **4.** Neu HC: Contribution of beta-lactamases to bacterial resistance and mechanisms to inhibit beta-lactamases. *Am J Med* 1985;79(suppl 5B):2-12.

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Bacteriological studies to determine the causative organisms and their susceptibility to *Augmentin* should be performed together with any indicated surgical procedures Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above Once results are known, adjust therapy, if appropriate

Contraindications: Patients with a history of allergic reactions to any penicillin, or patients with a history of *Augmentin*-associated cholestatic jaundice/hepatic dysfunction.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS BEFORE INITIATING THERAPY WITH *AUGMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.** Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis." After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. Use *Augmentin* cautiously in patients with evidence of hepatic dysfunction Hepatic toxicity associated with *Augmentin* use is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications (see CONTRAINDICATIONS and ADVERSE REACTIONS—*Liver*).

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients There are no data with *Augmentin* and allopurinol administered concurrently

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin* There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman

Adverse Reactions: *Augmentin* is generally well tolerated The majority of side effects observed in clinical trials were mild and transient, <3% of patients discontinued therapy because of them. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose Other less frequently reported reactions include abdominal discomfort, flatulence and headache

The following adverse reactions have been reported for ampicillin class antibiotics

Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis, mucocutaneous candidiasis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis). These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (see WARNINGS). A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. Interstitial nephritis and hematuria have been reported rarely Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*. Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely

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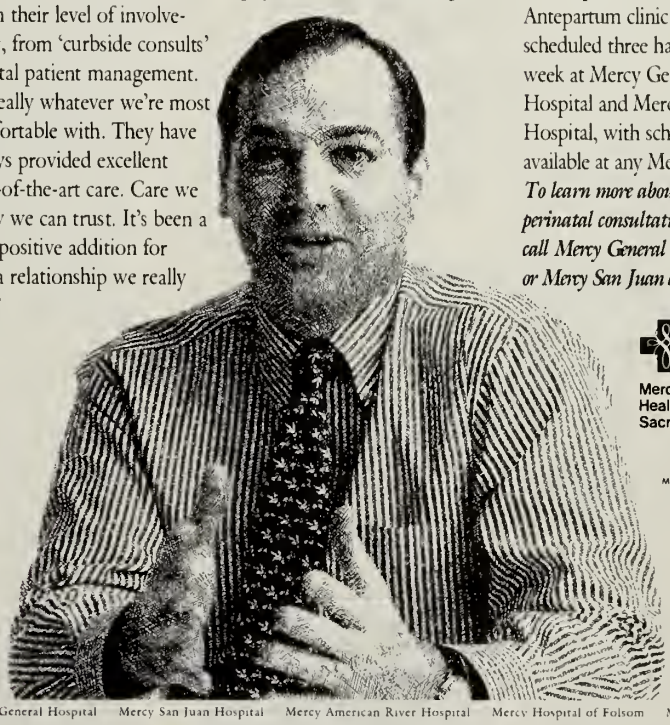

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Physician groups are concerned that legislation requiring physicians to report illegal immigrants to immigration authorities will delay curative care. In particular, patients with tuberculosis may delay seeking care for infectious symptoms and spread the disease. We surveyed 313 consecutive patients with active tuberculosis from 95 different facilities to examine the relationship of immigration-related variables, symptoms, and delay in seeking care. Most patients (71%) sought care for symptoms rather than as a result of the efforts of public health personnel to screen high-risk groups or to trace contacts of infectious persons. At least 20% of respondents lacked legal documents allowing them to reside in the United States. Few (6%) feared that going to a physician might lead to trouble with immigration authorities. Those who did were almost 4 times as likely to delay seeking care for more than 2 months, a period of time likely to result in disease transmission. Patients potentially exposed an average of 10 domestic and workplace contacts during the course of the delay. Any legislation that increases undocumented immigrants' fear that health care professionals will report them to immigration authorities may exacerbate the current tuberculosis epidemic.

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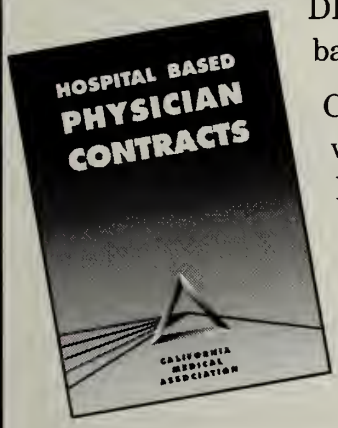

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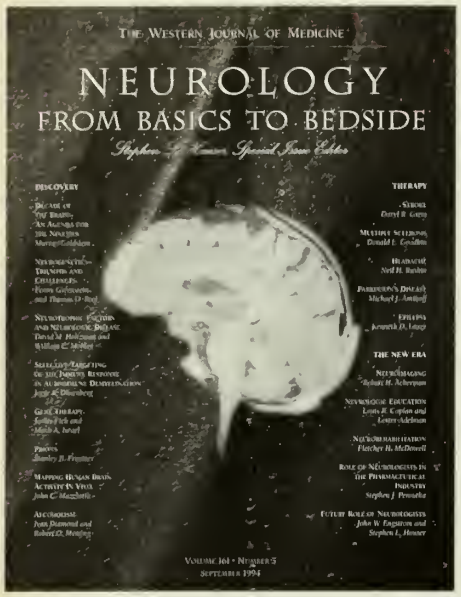

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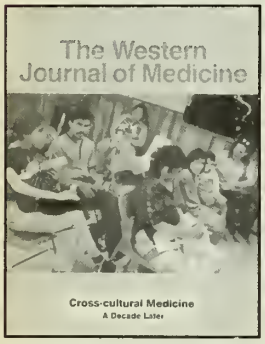

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PROGRAM PROFILE

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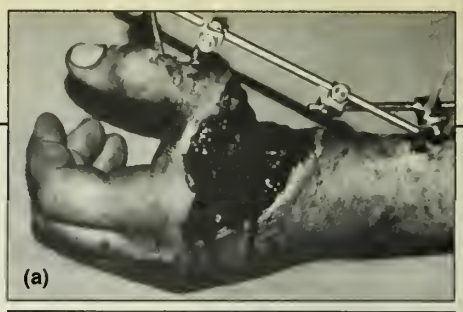

A 27-year-old who sustained a gunshot wound to the base of his thumb was left with (a) a composite defect including lost skin, muscle, tendon, nerve and bone; (b) simultaneous reconstruction of all these missing structures was successfully performed using a tissue flap from his opposite upper arm employing microsurgical techniques.

Microvascular reconstruction has dramatically expanded the field of plastic surgery, opening doors for subspecialists who perform radical resections for the ablation of tumors or who attempt salvage of extremities that have been severely traumatized.

The Reconstructive Surgery Team works closely with specialists in otolaryngology-head and neck surgery, neurosurgery, general surgery, orthopaedics, urology, oncology and rehabilitation. Together they incorporate a variety of procedures, blending innovative techniques that offer the greatest advantage for functional and aesthetic restoration, including:

Hand Surgery

Reconstructive hand surgery is a multifaceted discipline that incorporates techniques employed in several specialties: the treatment of bony injuries, the care of nerves and soft tissue, the restoration of mechanics — joints, tendons, and ligaments. Surgical specialists perform microsurgical replantation and reconstruction of complex hand injuries, and treat congenital hand deformities and hand burns.

USC University Hospital

USC UNIVERSITY HOSPITAL
Richard K. Eamer Medical Plaza
We're advancing medicine.
A National Medical Enterprises Medical Center

Reconstructive Microsurgery and Complex Wound Management

USC surgeons perform microsurgical free tissue transfer (using vascularized tissue flaps) to manage complex wounds which entails re-establishing circulation of the supplying arteries and draining veins between donor tissue and injury site.

Burn Reconstruction

Specialists in the secondary reconstruction of burn injuries use unique methods of restoring form and function. Surgeons have developed an operation that restores normal neck contour, and another that reconstructs ears, using materials which behave like living tissue. In facial reconstruction, they work to restore balance to the patient's features, focusing not only on skin coverage but also on the structure of the facial skeleton to compensate for the loss of soft tissue and scar contracture.

Treatment of Craniofacial Deformities

The oromandibular region is particularly complex. Through advances in techniques and instrumentation, reconstructive surgeons can move the forehead, change the position of the eyes, realign the jaws and reshape the underlying structure to make dramatic differences in craniofacial deformities.

UNIVERSITY
PLASTIC SURGEONS

B. Chandrasekhar, M.D.
Bill Dougherty, M.D.
Susan E. Downey, M.D.
John Gross, M.D.
Larry S. Nichter, M.D.
John F. Reinisch, M.D.
Randolph Sherman, M.D.
Gerald M. Sloan, M.D.
Tad Wellisz, M.D.

Reconstructive Breast Surgery

One alternative, the TRAM flap breast reconstruction procedure, involves the use of abdominal skin and muscles to form a new breast. Other options include autologous tissue replacement, implants, and tissue expanders followed by breast implant.

Post-Cancer Reconstruction

Patients who require extensive disfiguring tumor resection are benefitted by advances in microvascular techniques and osseointegrated implants for facial prosthetic reconstruction. In addition, musculoskeletal tumors in the upper and lower extremities that once required amputation may be treated through limb salvage procedures that incorporate antibiotic therapy, tumor resection, immediate implantation of bone allograft or endoprostheses, and microvascular coverage using free tissue transfer.

Close Communication With Referring Physicians

Members of the University Plastic Surgeons/ Center for Reconstructive Surgery are committed to maintaining close contact with referring physicians to ensure effective patient management for optimal recovery.

chool of Medicine

PHYSICIAN
ACCESS AND
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USC PHYSICIAN ACCESS AND COMMUNICATION EXCHANGE

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Designed by doctors for doctors as an easy, fast, convenient and free means to contact our faculty and services.

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☎ Information about research programs and medications

☎ Information about Continuing Medical Education (CME)

☎ Access to the extensive Norris Medical Library

☎ Assistance in arranging patient transfers for treatment or diagnosis, via helicopter transfer if necessary

☎ Exchanging information about referred patients

☎ Access to physicians at Childrens Hospital Los Angeles, Doheny Eye Institute, USC/Norris Cancer Center and USC University Hospital

☎ Physician referrals respected

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Continuing Medical Education

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 28-29—**Annual Southwestern Poison and Drug Symposium.** University of Arizona College of Medicine at the Aztec Inn, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

October 28-30—**Arrthymias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Camelback Inn, Scottsdale. Fri-Sun. Contact: Karen DeBont, (800) 421-3756.

November 3-6—**24th Annual Meeting: Musculoskeletal & MRI.** Maricopa Medical Center, Department of Radiology, at Camelback Inn, Scottsdale. Thurs-Sat. Contact: (602) 267-5366.

November 4-5—**Arizona Geriatric Society Annual Conference.** University of Arizona College of Medicine at the Ramada Inn Valley Hotel, Scottsdale. Fri-Sat. Contact: Lynne Mascarella, U of A.

November 4-5—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

November 4-5—**Hematology and Oncology for Primary Care Physicians.** Mayo Clinic-Scottsdale at the Orange Tree Golf Resort, Scottsdale. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

November 5-6—**Pelvic Anatomy Course.** University of Arizona College of Medicine at Arizona Health Sciences Center, Tucson. Sat-Sun. Contact: Lynne Mascarella, U of A.

November 7-11—**The Physician Management Seminar Series: Seminar I.** American College of Physician Executives at the Scottsdale Plaza Resort, Scottsdale. Mon-Fri. Contact: (800) 562-8088.

November 7-11—**The Physician Management Seminar Series: Seminar II.** American College of Physician Executives at the Scottsdale Plaza Resort, Scottsdale. Mon-Fri. Contact: (800) 562-8088.

November 10-12—**7th Annual Techniques in Gynecologic Surgery.** Mayo Clinic-Scottsdale at Marriott's Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

November 14-16—**Hand and Wrist Injuries in the Athlete.** American Society for Surgery of the Hand at Scottsdale. Mon-Wed. Contact: (303) 771-9236.

November 17-19—**Pediatric Orthopaedics: A Comprehensive Course.** American Academy of Orthopaedic Surgeons at The Pointe Hilton Resort at Squaw Peak, Phoenix. Thurs-Sat. Contact: AAOS, (708) 823-7186.

November 18—**Cost Effective Treatment of Arthritis Patients.** University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

December 2-3—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

December 2-4—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Hyatt Regency, Scottsdale. Fri-Sun. Contact: Karen DeBont, (800) 421-3756.

January 12-13—**2nd Annual Current Topics in Critical Care Medicine.** Mayo Clinic-Scottsdale at the Ritz-Carlton Hotel, Phoenix. Thurs-Fri. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 14-15—**5th Annual Current Topics in Anesthesiology.** Mayo Clinic-Scottsdale at the Ritz-Carlton Hotel, Phoenix. Sat-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 20-22—**Electromyography in Clinical Practice.** Mayo Clinic-Scottsdale. Fri-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 6-10—**Psychopharmacology Review Course.** University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Mon-Fri. Contact: Lynne Mascarella, U of A.

February 12-16—**International Congress VIII on Endovascular Interventions: Breaking the Barriers.** American College of Angiology at the Phoenician Resort, Scottsdale. Sun-Thurs. Contact: (602) 266-2200.

February 16-18—**Mayo Interactive Surgical Symposium.** Mayo Clinic-Scottsdale at the Orange Tree Golf and Conference Resort, Scottsdale. Thurs-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 19-22—**Practical Radiology.** University of Arizona College of Medicine at Loews Ventana Canyon Resort, Tucson. Sun-Wed. Contact: Lynne Mascarella, U of A.

February 23-24—**Hepatology Update 1995.** Mayo Clinic-Scottsdale at the Ritz-Carlton, Phoenix. Thurs-Fri. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 24-25—**Mayo Plastic Surgery Symposium.** Mayo Clinic-Scottsdale at the Ritz-Carlton Hotel, Phoenix. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 24-26—**1995 Scientific Assembly—American Academy of Family Practice.** The Pointe Hilton at Tapatio Cliffs, Phoenix. Fri-Sun. Contact: American Academy of Family Practice, Arizona Chapter, (602) 249-2021.

March 5-9—**Radiology in the Desert: Practical Aspects of Radiology and Imaging.** University of Michigan Medical School at Marriott's Camelback Inn Resort, Scottsdale. Sun-Thurs. Contact: Lynne Mascarella, U of A.

April 5-8—**Primary Care Update.** University of Arizona College of Medicine at the Tucson East Hilton. Wed-Sat. Contact: Lynne Mascarella, U of A.

May 7-11—**Fundamental Principles of Pharmacokinetics and Toxicokinetics for the Industrial Scientist.** University of Arizona College of Medicine at the Westward Look Resort, Tucson. Sun-Thurs. Contact: Lynne Mascarella, U of A.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832; (800) 328-5868 or (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

November 11-13—**Anesthesiology Update: 1994.** UCD at Monterey Plaza, Monterey. Fri-Sun. 14 hrs. $325. Contact: UCD.

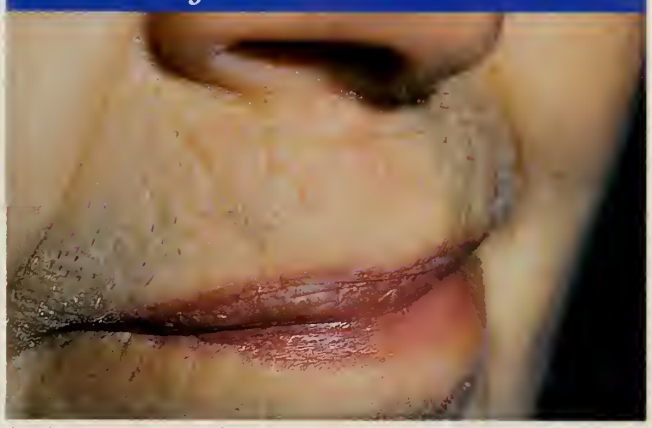
(Continued on Page 361)

Which Therapy Cured This Infection?

❑ oral cephalosporin ❑ oral erythromycin ❑ topical mupirocin

Pretreatment

After 12 days' treatment



Actual unretouched physician file photos of 71-year-old patient with impetigo

Presentation:
Classic erythematous yellow-crusted lesions

Diagnosis: Impetigo

Observations:
Resolution of infection

Please see complete prescribing information on adjacent page.

Turn page for the answer.

CONTINUING MEDICAL EDUCATION

(Continued from Page 360)

November 18-19—**4th Annual Pain Conference.** UCD at Inn at Napa Valley. Fri-Sat. 11 hrs. $300. Contact: UCD.

January 4-7—**Anesthesia Update.** UCSD at Hotel del Coronado, San Diego. Mon-Sat. 21 hrs. $350. Contact: UCSD.

February 3-5—**33rd Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: David Steward, MD, Director, PO Box 54700, Los Angeles 90054. (213) 669-2262.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center. PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs, (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

CARDIOLOGY

October 27-30—**East Visits West: Coronary Interventions 1994.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sun. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, 403C, La Jolla 92037. (619) 554-8556.

October 29—**Arrhythmia Update '94.** Hospital of the Good Samaritan Los Angeles at Moseley-Salvatori Conference Center. Sat. 6 hrs. Contact: Anil K. Bhandari, MD, (213) 977-2335.

November 4-5—**Update in Electrocardiography & Arrhthymias.** UCSF at Ritz-Carlton, San Francisco. Fri-Sat. 8 hrs. $150. Contact: UCSF.

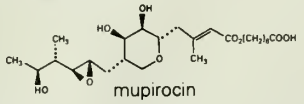
November 18-20—**Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. 11 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

(Continued on Page 362)

Bactroban®
mupirocin

PRESCRIBING INFORMATION
BACTROBAN®
brand of
mupirocin ointment 2%
For Dermatologic Use

DESCRIPTION
Each gram of *Bactroban* Ointment 2% contains 20 mg mupirocin in a bland water miscible ointment base (polyethylene glycol ointment, N.F.) consisting of polyethylene glycol 400 and polyethylene glycol 3350. Mupirocin is a naturally occurring antibiotic. The chemical name is (*E*)-(2*S*,3*R*,4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxy-β-methyl-2*H*-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid. The chemical structure is:



mupirocin

CLINICAL PHARMACOLOGY
Mupirocin is produced by fermentation of the organism *Pseudomonas fluorescens*. Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer-RNA synthetase. Due to this mode of action, mupirocin shows no cross resistance with chloramphenicol, erythromycin, fusidic acid, gentamicin, lincomycin, methicillin, neomycin, novobiocin, penicillin, streptomycin, and tetracycline.

Application of ^{14}C-labeled mupirocin ointment to the lower arm of normal male subjects followed by occlusion for 24 hours showed no measurable systemic absorption (<1.1 nanogram mupirocin per milliliter of whole blood). Measurable radioactivity was present in the stratum corneum of these subjects 72 hours after application.

Microbiology: The following bacteria are susceptible to the action of mupirocin *in vitro*: the aerobic isolates of *Staphylococcus aureus* (including methicillin-resistant and β-lactamase producing strains), *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, and *Streptococcus pyogenes*.

Only the organisms listed in the INDICATIONS AND USAGE section have been shown to be clinically susceptible to mupirocin.

INDICATIONS AND USAGE
Bactroban (mupirocin) Ointment is indicated for the topical treatment of impetigo due to: *Staphylococcus aureus*, beta-hemolytic *Streptococcus**, and *Streptococcus pyogenes*.

*Efficacy for this organism in this organ system was studied in fewer than ten infections.

CONTRAINDICATIONS
This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components.

WARNINGS
Bactroban Ointment is not for ophthalmic use.

PRECAUTIONS
If a reaction suggesting sensitivity or chemical irritation should occur with the use of *Bactroban* Ointment, treatment should be discontinued and appropriate alternative therapy for the infection instituted.

As with other antibacterial products prolonged use may result in overgrowth of nonsusceptible organisms, including fungi.

Bactroban is not formulated for use on mucosal surfaces. Intranasal use has been associated with isolated reports of stinging and drying.

Polyethylene glycol can be absorbed from open wounds and damaged skin and is excreted by the kidneys. In common with other polyethylene glycol-based ointments, *Bactroban* should not be used in conditions where absorption of large quantities of polyethylene glycol is possible, especially if there is evidence of moderate or severe renal impairment.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at systemic doses, i.e., orally, subcutaneously, and intramuscularly, up to 100 times the human topical dose and have revealed no evidence of impaired fertility or harm to the fetus due to mupirocin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether *Bactroban* is present in breast milk. Nursing should be temporarily discontinued while using *Bactroban*.

ADVERSE REACTIONS
The following local adverse reactions have been reported in connection with the use of *Bactroban* Ointment: burning, stinging, or pain in 1.5% of patients; itching in 1% of patients; rash, nausea, erythema, dry skin, tenderness, swelling, contact dermatitis, and increased exudate in less than 1% of patients.

DOSAGE AND ADMINISTRATION
A small amount of *Bactroban* Ointment should be applied to the affected area three times daily. The area treated may be covered with a gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.

HOW SUPPLIED
Bactroban (mupirocin) Ointment 2% is supplied in 1 gram Single Unit Packages of 50 and in 15 gram and 30 gram tubes.

NDC 0029-1525-15 (1 gram SUP)
NDC 0029-1525-22 (15 gram tube)
NDC 0029-1525-25 (30 gram tube)

Store between 15° and 30°C (59° and 86°F).

DATE OF ISSUANCE MAY 1992

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Manufactured by RSR Laboratories
Bristol, TN 37620 for
SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

BC:L3B

SB SmithKline Beecham Pharmaceuticals

CONTINUING MEDICAL EDUCATION

(Continued from Page 361)

December 9-11—**12th Annual Advances in Heart Disease.** American College of Cardiology at San Francisco. Fri-Sun. 16.5 hrs. Contact: ACC, 911 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

DERMATOLOGY

November 11-13—**5th Annual Cutaneous Malignancies: 1994 Skin Cancer Update.** Scripps Clinic and Research Foundation at Schaetzel Center for Health Education, La Jolla. Fri-Sun. 16 hrs. Contact: Scripps, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

October 31-November 4—**Topics in Emergency Medicine**. UCSF at Miyako Hotel, San Francisco. Mon-Fri. 32 hrs. $575. Contact: UCSF.

November 7-11—**Emergency Medicine Symposium.** UCSD at La Jolla Marriott, San Diego. Mon-Fri. 32 hrs. $495. Contact: UCSD.

December 4-9—**15th Annual Conference: Current Concepts in Emergency Care.** American College of Emergency Physicians at Maui Intercontinental Resort, Hawaii. Sun-Fri. 20 hrs. Contact: Kailani World Travel, 4192 Meridian Ave, Box 9751, Bellingham, WA 98227. (800) 544-9269 or (206) 671-1800.

December 12-16—**Emergency Medicine Symposium.** UCSD at Basic Science Building. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 16-20—**Emergency Medicine Symposium.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 24-29—**California Trauma Conference.** UCSD at Hyatt Regency, San Diego. Tues-Sun 20 hrs. $395.Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

November 5—**Neurology for Primary Care.** UCD at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. $95. Contact: UCD.

November 5—**What to Do About Hypertension in 1995.** American Society of Hypertension at Hotel Nikko, Beverly Hills. Sat. 4 hrs. Contact: ASH, 515 Madison Ave, #1212, New York, NY 10022. (212) 644-0650.

December 9-11—**Neurology for the Non-Neurologist.** American College of Emergency Physicians at Desert Inn, Las Vegas, Nevada. Fri-Sun. 12 hrs. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

December 24-29—**Advances in Medicine '94.** American Academy of Family Physicians and Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Lahaina, Maui, Hawaii. Sat-Thurs. 16 hrs. Contact: Joe Harrison, MD, PO Box 10185, Lahaina, HI 96761. (808) 878-6757.

January 20-22—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 2-4—**Neurology for the Non-Neurologists.** UCSD at Doubletree Hotel, San Diego. Thurs-Sat. Contact: UCSD.

February 14-19—**The Practicing Physician's Approach to the Difficult Headache Patient.** Dannemiller Memorial Educational Foundation at Marriott's Rancho Las Palmas Resort and Country Club, Rancho Mirage. Tues-Sun. Contact: Diamond Headache Clinic, 5252 N Western Ave, Chicago, IL 60625. (312) 907-6226.

February 17-19—**Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

(Continued on Page 363)

❑ oral cephalosporin ❑ oral erythromycin ✓ topical mupirocin

Actual unretouched physician file photos of 71-year-old patient with impetigo

For Impetigo

Bactroban® mupirocin

Power of an oral antibiotic
Safety of a topical

SB SmithKline Beecham Pharmaceuticals ©SmithKline Beecham, 1994 Philadelphia, PA 19101

Please see complete prescribing information on adjacent page.

CONTINUING MEDICAL EDUCATION

(Continued from Page 362)

GERIATRICS

October 29—**Chronic Illness, Depression and the Elderly.** UCSF Mount Zion Center on Aging at UCSF Laurel Heights Conference Center. Sat. Contact: Mary Henderson, RN, Mount Zion Center on Aging, (415) 750-4170.

November 7-9—**Geriatrics Update: 1994.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Mon-Wed. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INFECTIOUS DISEASE

November 4-5—**Kuzell Institute Symposia for Rheumatology and Infectious Diseases.** California Pacific Medical Center at Ana Hotel, San Francisco. Fri-Sat. 12 hrs. $60. Contact: Kaura Johnson, CPMC, 2485 Clay St, San Francisco. (415) 923-3242.

November 4-6—**Advances in Infectious Disease.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

November 19-20—**2nd Annual Advances in Clinical Neurosciences.** Hospital of the Good Samaritan at Rancho Las Palmas Resort, Rancho Mirage. Sat-Sun. 11.5 hrs. Contact: Christopher M. Duma, MD, (213) 977-2335.

December 4—**Complications in Diabetes.** USC at Red Lion Hotel, Glendale. Sun. 5.5 hrs. $45. Contact: USC.

February 1-4—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Hyatt, San Diego. Wed-Sat. 35 hrs. $500. Contact: UCSD.

March 17-23—**Internal Medicine 1995: A Comprehensive Review.** Continuing Medical Education Associates at Hotel del Coronado. Fri-Thurs. 54 hrs. $695. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

OB/GYN

October 29—**Menopause and Hormone Replacement.** USC at Universal Hilton Hotel, Universal City. Sat. 4.25 hrs. $25. Contact: USC.

November 12—**Breast Cancer Management.** USC at Health Sciences Campus. Sat. 5 hrs. $35. Contact: USC.

December 1-3—**Obstetrics and Gynecology Conference.** University of Nebraska Medical Center at Bally's, Las Vegas, Nevada. Thurs-Sat. $275. Contact: UNMC, 600 S 42nd St, Omaha, NE 68198-5651. (800) 642-1095 or (402) 559-4152.

February 9-12—**50th Annual Postgraduate OB/GYN Assembly.** Obstetrical and Gynecological Assembly of Southern California at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OGASC, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

OCCUPATIONAL/ENVIRONMENTAL

October 24-28—**Occupational and Environmental Medicine.** UCSF at Ana Hotel, San Francisco. Mon-Fri. 40 hrs. $725. Contact: UCSF.

ONCOLOGY

November 10-12—**New Directions in Antiviral Chemotherapy.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 18 hrs. $325. Contact: UCSF.

(Continued on Page 366)

(Continued from Page 357)

410 Bone Imaging Using Single-Proton Emission Computed Tomography
GARY F. GATES, MD

411 Positron Emission Tomographic Oncology
MICHAEL A. LAWSON, MD

412 Monoclonal Antibody Imaging of Colorectal and Ovarian Cancer
MICHAEL K. HASEMAN, MD

412 Regional Cerebral Blood Flow and Cocaine Abuse
KATE M. BELL, MD; NORA MILNE, MD; and KENNETH P. LYONS, MD

413 Technetium Tc 99m Sestamibi for Parathyroid Imaging
EUGENE T. MORITA, MD; WALTER P. KWAN, MD; and ORLO H. CLARK, MD

ALERTS, NOTICES, AND CASE REPORTS

415 *Mycobacterium avium-intracellulare* and Acute Abdominal Pain
EDWARD M. BOYLE Jr, MD; KENTON STEPHENS Jr, MD; and TIMOTHY H. POHLMAN, MD
From the Department of Surgery, Harborview Medical Center, University of Washington School of Medicine, Seattle.

417 Lactic Acidosis in a Patient With Multiple Myeloma
BARRY A. MIZOCK, MD, and JORGE N. GLASS, MD
From the Division of Critical Care Medicine and Department of Medicine, Cook County Hospital, and the University of Health Sciences/Chicago Medical School, Chicago, Illinois.

418 Hemorrhagic Fever With Renal Syndrome in California
WILLIAM MORRIS, MD, MPH; MOLLY FAINSTAT, MD; TRACEY ROBINSON, MD; and ROBERT HOO, MD
From the Departments of Internal Medicine and Rheumatology, Santa Clara Valley Medical Center, San Jose, California.

COMMENTARY

422 Case Report 23289 and Medical Economics
MICHAEL J. HENNESSY, MD
Dr Hennessy is in private practice in orthopedic surgery in San Diego, California.

424 Health Care Costs and Technologies
DONALD KENNEDY, PhD
From the Institute for International Studies, Stanford University, Stanford, California. Dr Kennedy is President Emeritus and Bing Professor of Environmental Science.

EDITORIAL

426 Dilemma of High-Tech Care for High-Risk Patients
MARVIN L. AUERBACK, MD
From the Foster City Pediatric Medical Group, Foster City, California.

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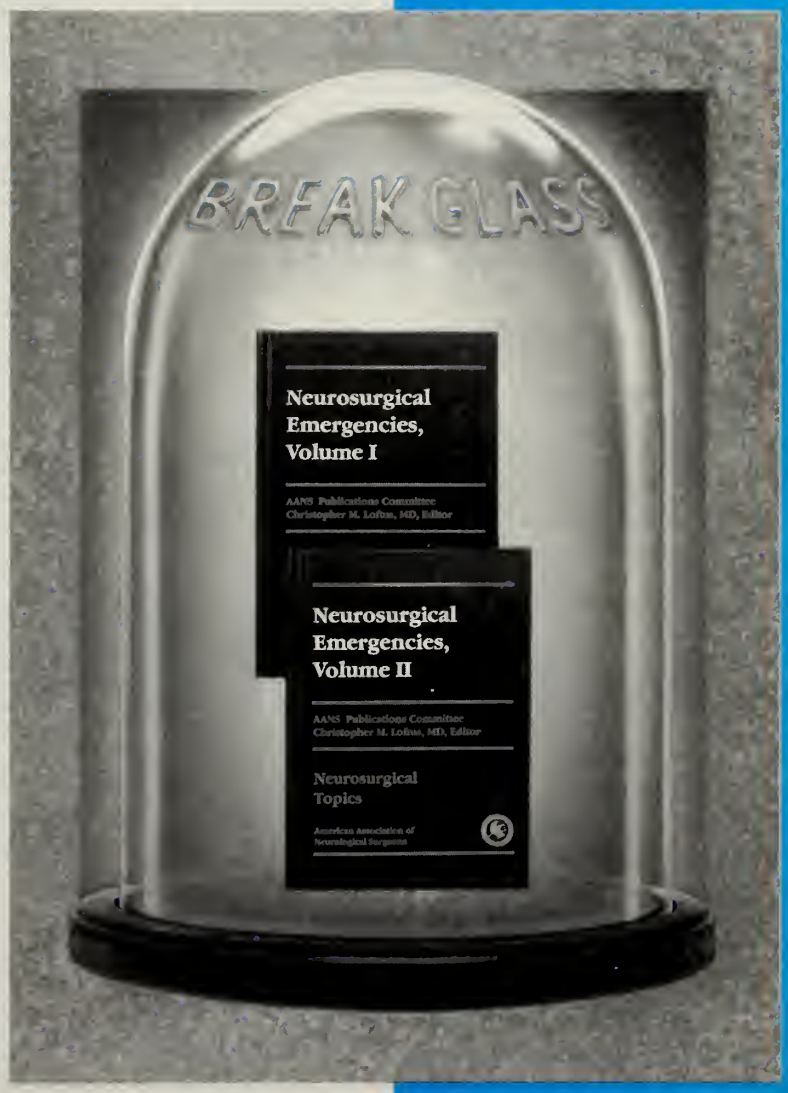

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CONTINUING MEDICAL EDUCATION

(Continued from Page 363)

February 20-23—**Clinical Hematology and Oncology: 1995.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 28 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OPHTHALMOLOGY

December 8-10—**New and Practical Approaches to Glaucoma Management.** UCSF at Ritz-Carlton Hotel and UCSF, San Francisco. Thurs-Sat. 13.5 hrs. $200-$395. Contact: UCSF.

December 9-10—**1st Annual West Coast Cosmetic Eyelid Rejuvenation Symposium.** Medical Education Resources at Beverly Hilton, Beverly Hills. Fri-Sat. 14 hrs. $575. Contact: Angela O'Mara, (714) 760-1522.

January 14—**Primary Care Ophthalmology.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

OTOLARYNGOLOGY

November 3-5—**Otolaryngology Update: 1994.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17 hrs. $425. Contact: UCSF.

November 13-18, December 10-15—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 53 hrs. $875-$1,100. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

PATHOLOGY

November 13-16—**Clinical Microbiology Update.** American Society of Clinical Pathologists at Pan Pacific Hotel, San Diego. Sun-Wed. Contact: ASCP, 2100 W Harrison St, Chicago, IL 60612-3798. (800) 621-4142.

December 5-7—**Soft Tissue Pathology: Conceptual and Practical Approaches to Diagnosis.** American Society of Clinical Pathologists at Surf and Sand Hotel, Laguna Beach. Mon-Wed. Contact: ASCP, 2100 W Harrison St, Chicago, IL 60612. (800) 621-4142.

PEDIATRICS

October 29—**Ambulatory Pediatrics.** UCD at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. $95. Contact: UCD.

October 29—**Pediatric Otology Update 1994.** Children's Hospital Oakland. Sat.7.5 hrs./$65. Contact: Hearing Institute Foundation, 2120 Forest Ave, #2, San Jose 95128. (408) 288-7777.

December 1-4—**Society of ENT Advances in Children.** UCD at Radisson Hotel, Sacramento. Thurs-Sun. 10 hrs. Contact: UCD.

December 3—**13th Annual Binational Pediatric Conference.** Children's Hospital San Diego and American Academy of Pediatrics at Mercy Hospital Educational Center, San Diego. Sat. $45. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

December 3-4—**Stabilization and Management of the Critically Ill Child.** UCSF at Mark Hopkins Hotel, San Francisco. Sat-Sun. 9 hrs. $250. Contact: UCSF.

January 21-28—**Pediatric Emergencies.** UCSD at Kona, Hawaii. 21 hrs. $460. Contact: UCSD.

January 23-27—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital San Diego at Town and Country Hotel, San Diego. Mon-Fri. $395. Contact: Children's Hospital, MC 5016, 3020 Children's Way, San Diego 92123. (619) 495-4940.

February 20-22—**Pediatrics Update 1995.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 3-5—**Current Concepts in Pediatric Medicine.** Children's Hospital San Diego at Catamaran Resort Hotel, San Diego. Fri-Sun. $365. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

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November

November 8, 1994
L.A. Cardiology Society Evening Forum
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David S. Cannom, M.D., Course Director

November 17, 1994
Gastroenterology Endoscopy Evening
"Barretts Esophagus—Why All The Excitement?"
Wilfred M. Weinstein, M.D.,
Priya Jamidar, M.D., & Peter Nair, M.D., Course Directors

November 19-20, 1994
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8 AM- 2 PM
Deane B. "Skip" Jacques, M.D., Oleg V. Kopyov, M.D., Ph.D., & Christopher M. Duma, M.D., Course Directors
Rancho Las Palmas Resort, Rancho Mirage, CA

November 30, 1994
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Anil Bhandari, M.D. & Peter Lorber, M.D., Course Directors

December

December 1, 1994
Perinatal Evening Lecture
"Fetal Lung Maturation Strategies"
Alan Jobe, M.D.
Robert Israel, M.D., T. Murphy Goodwin, M.D., & R. Rangasamy, M.D., Course Directors

CONTINUING MEDICAL EDUCATION

(Continued from Page 366)

PHYSICAL MEDICINE/REHABILITATION

October 8-12—**56th Annual Assembly, American Academy of Physical Medicine and Rehabilitation** at Anaheim Hilton Hotel and Towers and Anaheim Convention Center. Sun-Wed. Contact: AAPMR, 122 S Michigan Ave, Ste 1300, Chicago, IL 60603-6107. (312) 922-9366.

PSYCHIATRY

November 19—**Treatment of Depression.** USC at Red Lion Hotel, Glendale. Sat. 6 hrs. $25. Contact: USC.

January 22-27—**21st Annual Midwinter Program for Psychiatrists.** UCD at Incline Village, Nevada. Sun-Fri. 25 hrs. Contact: UCD.

PULMONARY MEDICINE

February 3-5—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Sheraton Desert Inn, Las Vegas, Nevada. Fri-Sun. 12 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528.

RADIOLOGY

October 31–November 4—**Diagnostic Radiology Seminars.** UCSF at Ritz-Carlton Kapalua, Maui, Hawaii. Mon-Fri. 26 hrs. $595. Contact: UCSF.

November 14-18—**A Practical Approach to Breast Imaging.** UCSF at Ritz-Carlton, Rancho Mirage. Mon-Fri. 20 hrs. $595. Contact: UCSF.

December 8-10—**Magnetic Resonance Angiography in Clinical Practice with CTA Correlation.** UCSF at Ritz-Carlton, Rancho Mirage. Thurs-Sat. 12.5 hrs. $425. Contact: UCSF.

December 11-16—**A Practical Approach to Breast Imaging.** UCSF at Ritz-Carlton Kapalua, Maui, Hawaii. Sun-Fri. 20 hrs. $595. Contact: UCSF.

March 5-9—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado. Sun-Thurs. 30 hrs. $595. Contact: UCSD.

SLEEP MEDICINE

January 28—**Sleep Medicine: Practices for the 21st Century.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

SURGERY

October 29—**Suture Workshop.** Sutter Community Hospitals at Sacramento. Sat. Contact: Catherine Davis, 2800 L St, 6th Fl, Sacramento 95816. (800) 777-0231.

November 11-12 —**Endoscopic Surgery.** USC at Health Sciences Campus. Fri-Sat. 15.75 hrs. $1500. Contact: USC.

December 1-2—**Laparoscopic Colon and Rectal Surgery.** USC at Health Sciences Campus, Los Angeles. Thurs-Fri. $1800. Contact: USC.

December 8-9—**13th Annual Neurosurgical Nurses' Conference.** UCSF at Hyatt Regency Embarcadero, San Francisco. Thurs-Fri. 13.5 hrs. $325. Contact: UCSF.

January 13-14—**What's New in General Surgery: 17th Annual Postgraduate Course.** UCD at Hyatt Hotel, Sacramento. 15 hrs. Contact: UCD.

January 13-15 —**Annual Meeting of the California Association of Neurological Surgeons:** Health Care Reform. California Association of Neurological Surgeons at Four Seasons Hotel, Newport Beach. Fri-Sun. 7 hrs. Laurie Alexander, (916) 971-3524.

February 6-10—**18th Annual San Diego Postgraduate Assembly in Surgery.** UCSD at Hyatt Islandia, San Diego. Mon-Fri. 26 hrs. $475. Contact: UCSD.

February 11-12—**Endoscopic Plastic Surgery and Beyond.** UCSD at BSB and Thornton Hospital, La Jolla. Sat-Sun. 13 hrs. $1250. Contact: UCSD.

GENERAL/MULTIDISCIPLINARY

October 27-30—**1994 CME/Golf Meeting.** Nevada Academy of Family Physicians at Sheraton Desert Inn Hotel & Casino, Las Vegas. Thurs-Sun. 21 hrs. Contact: Barbara Bolling, NAFP, PO Box 27713, Las Vegas, NV 89126-1713. (702) 647-0117.

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January 19-22—**Medicine Meets Virtual Reality II: Interactive Technology & Healthcare.** UCSD. Thurs-Sat. Contact: UCSD.

January 31-February 4—**Critical Care by Design.** Society of Critical Care Medicine at Moscone Center, San Francisco. Tues-Sat. 30.5 hrs. $600. Contact: SCCM, 8101 E Kaiser Blvd, Anaheim 92808-2259. (714) 282-6000.

February 13-17—**Physician Heal Thyself.** UCSD at Sheraton Harbor Island, San Diego. Mon-Fri. Contact: UCSD.

February 16-19—**2nd International Congress on Vitamins and Biofactors in Life Science.** Thurs-Sun. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 18-21—**Molecular Approaches to Laboratory Diagnosis.** UCSF at Ritz-Carlton, San Francisco. Sat-Tues. Contact: UCSF.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

October 24-28—**Prevention in Practice: Workplace Health in the 21st Century.** American College of Occupational and Environmental Medicine at Denver Marriott City Center, Denver. Mon-Fri. Contact: ACOEM, (708) 228-6850.

January 28-February 2—**24th Annual Mid-Winter Conference of Colorado Ophthalmological Society.** Sheraton Steamboat, Steamboat Springs. Sun-Thurs. Contact: David R. Scott, (800) 394-4968.

February 20-24—**19th Midwinter Symposium on Practice Surgical Challenges in Otolaryngology.** University of Illinois College of Medicine at Snowmass. Mon-Fri. Contact: Jane Whitener, (312) 996-5751.

February 26-March 3—**Ninth Annual Cardiology for the Clinician Conference: Practical Guidelines for Merging Advances in Cardiology and Bedside Medicine.** University of Illinois College of Medicine at Snowmass. Mon-Fri. Contact: Sue Talbert, (312) 996-4631.

March 5-10—15th **Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Medical Center, (402) 559-4152 or (800) 642-1095; FAX (402) 559-5915.

July 28-August 1—**80th Annual Summer Conference.** Colorado Ophthalmological Society at Sheraton Steamboat Resort, Steamboat Springs. Fri-Tues. Contact: David R. Scott, (800) 394-4968; FAX (303) 438-9602.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 270-6761.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 28-29—**ECG Interpretation for the Primary Care Physician.** Journal Center, Albuquerque. Fri-Sun. Contact: Tracy L. Green, New Mexico Heart Clinic, (505) 841-1000.

October 28-29—**New Mexico Orthopaedic Association 1994 Annual Meeting.** Hyatt Regency, Albuquerque. Fri-Sun. Contact: Lynette Hanks, NMOA, (800) 748-1596.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

December 2—**AIDS and Related Diseases.** University of Utah School of Medicine. Fri. Contact: UUSM.

December 3-8—**Intensive MR Imaging and Neuroradiology.** University of Utah School of Medicine at the Marriott Hotel, Salt Lake City. Sat-Thurs. 45 hrs; $1,200. Contact: UUSM.

January 17-22—**Advances in Craniofacial/Oculoplastic and Facial Aesthetic Surgery.** University of Utah School of Medicine at the Cliff Lodge at Snowbird. Tues-Sun. 24 hrs. $525. Contact: UUSM.

January 23-27—**Workshops in Advances MR Imaging, Head and Neck Imaging, and Neuroradiology.** University of Utah School of Medicine. Mon-Fri. Contact: UUSM.

February 6-10—**Surgical Pathology.** University of Utah School of Medicine at the Yarrow Hotel, Park City. Mon-Fri. 20 hrs. $550. Contact: UUSM.

February 20-24—**Workshops in Advanced MR Imaging, Head and Neck Imaging, and Neuroradiology.** University of Utah School of Medicine. Mon-Fri. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

(Continued on Page 372)

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WESTIN SOUTH COAST PLAZA HOTEL
COSTA MESA, CALIFORNIA

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Laser Bronchoscopy, Stents, Brachytherapy
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LONG BEACH, CALIFORNIA

Thoracoscopy for the Pulmonologist
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January, 1995

10th Annual Perinatal Symposium
January 11-15, 1995
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BEAVER CREEK, COLORADO

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HYATT REGENCY GRAND CAYMAN
BRITISH WEST INDIES

February, 1995

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February 18-20, 1995
LONG BEACH MEMORIAL MEDICAL CENTER
LONG BEACH, CALIFORNIA

16th Annual Symposium—Current Topics in Obstetrics
February 18-25, 1995
THE GANT CONDOMINIUMS
ASPEN, COLORADO

April, 1995

Advanced Urogynecology and Pelvic Surgery
April 5-9, 1995
MARQUIS HOTEL AND VILLAS
PALM SPRINGS, CALIFORNIA

4th Annual OB/GYN Ultrasound—The State of the Art
April 11-14, 1995
WESTIN RESORT
MAUI, HAWAII

20th Annual Care of the Sick Newborn Symposium
April 26-28, 1995
HYATT REGENCY HOTEL
LONG BEACH, CALIFORNIA

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May 19, 1995
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CME CREDITS VARY PER COURSE.

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CORRESPONDENCE

427 **Laparoscopic Colectomy—An Initial Experience**
ROBERT W. BEART Jr, MD, and RICHARD T. SCHLINKERT, MD

427 **Recurrent Hyperthermia Due to Lovastatin**
WILLIAM R. von POHLE, MD

428 **Rochalimaea—A Cosmopolitan Zoonosia?**
PATRICK E. OLSON, MD; JEAN G. CREEK, MT; and MARK R. WALLACE, MD

428 **Communicating With Patients**
FREDERIC W. PLATT, MD

LESSONS FROM THE PRACTICE

429 **Who's in Charge Here, Anyway?**
ROLLIN ODELL Jr, MD
Dr Odell is in private practice in radiation oncology in Orinda, California.

431 **Treachery of the Hysterical Diagnosis**
LARRY E. DAVIS, MD
From the Neurology Service, Department of Veterans Affairs Medical Center, and the Departments of Neurology and Microbiology, University of New Mexico School of Medicine, Albuquerque, New Mexico.

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444 **Western State Medical Associations' Meetings**

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Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

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How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

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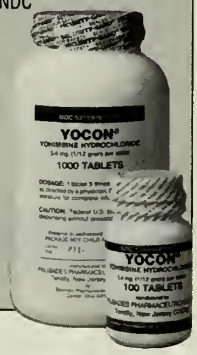

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Articles

Does Fear of Immigration Authorities Deter Tuberculosis Patients From Seeking Care?

STEVEN ASCH, MD, MPH; BARBARA LEAKE, PhD; *and*
LILLIAN GELBERG, MD, *Los Angeles, California*

Physician groups are concerned that legislation requiring physicians to report illegal immigrants to immigration authorities will delay curative care. In particular, patients with tuberculosis may delay seeking care for infectious symptoms and spread the disease. We surveyed 313 consecutive patients with active tuberculosis from 95 different facilities to examine the relationship of immigration-related variables, symptoms, and delay in seeking care. Most patients (71%) sought care for symptoms rather than as a result of the efforts of public health personnel to screen high-risk groups or to trace contacts of infectious persons. At least 20% of respondents lacked legal documents allowing them to reside in the United States. Few (6%) feared that going to a physician might lead to trouble with immigration authorities. Those who did were almost 4 times as likely to delay seeking care for more than 2 months, a period of time likely to result in disease transmission. Patients potentially exposed an average of 10 domestic and workplace contacts during the course of the delay. Any legislation that increases undocumented immigrants' fear that health care professionals will report them to immigration authorities may exacerbate the current tuberculosis epidemic.

(Asch S, Leake B, Gelberg L: Does fear of immigration authorities deter tuberculosis patients from seeking care? West J Med 1994; 161:373-376)

Although the incidence of tuberculosis has declined in the United States throughout this century, the disease remains prevalent in much of the developing world. Its recent resurgence has coincided with rising immigration rates from these areas of high prevalence.[1] High rates of immigration have historically engendered attempts to limit immigrants' access to social services, and several states are currently considering legislation denying publicly funded health care to undocumented immigrants. Public health authorities and physician groups have expressed concern that legislation requiring providers of publicly funded services to report illegal immigrants to immigration authorities will delay curative care for infectious diseases and exacerbate the tuberculosis epidemic (B. Hayward, "Coalition Vows to Fight Immigration Initiative," *The Sacramento Bee*, June 23, 1994, p A3). Even though some policies may exclude public health functions like tuberculosis-case tracking from the list of services requiring immigration papers, these patients may not recognize their symptoms as indicative of tuberculosis. They might then delay seeking care, thus allowing the disease to spread.

Few data exist regarding the proportion of tuberculosis patients who will be affected by immigration legislation. In the United States, 22% of patients with tuberculosis were born in other countries.[2] Few studies have examined what proportion lack legal immigration papers. Similarly, basic measures of acculturation such as linguistic proficiency or length of time in the United States are lacking for patients with tuberculosis. Nor has any study directly examined the prevalence of fear of immigration authorities in these patients. Even if few patients have such fear under the current law, how long they delay seeking care will shed light on the extent to which policies that increase fear will increase delay. Yet no studies of patients with tuberculosis have examined the effect of immigration and cultural variables on delay.

If the public health system diagnoses most cases of tuberculosis as a result of contact tracing or screening high-risk groups, the effect of immigration on the delay in seeking care becomes less crucial to ascertain. Recent studies have cast doubt on the efficacy of traditional case-tracking methods.[3] Yet little is known about whether patients with tuberculosis come to attention because they seek care for symptoms or because public health personnel identify them.

Los Angeles, California, lies at one of the epicenters of the tuberculosis epidemic—second only to New York City. Unlike the nation as a whole, immigrants make up most of the active tuberculosis cases in Los Angeles,

From the Division of General Internal Medicine, Los Angeles County and University of Southern California Medical Center (Dr Asch), and Divisions of General Internal Medicine (Drs Asch and Leake) and Family Medicine (Dr Gelberg), University of California, Los Angeles, School of Medicine.

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making it an ideal site from which to generalize to other areas considering limiting undocumented immigrants' access to health services.[4] We report the results of a Los Angeles County registry-based survey examining the relationship of symptoms, immigration-related variables, and tuberculosis patients' delay in seeking medical care.

Methods

Study Population

The law requires health care professionals, laboratories, and governmental agencies to report all suspected and confirmed cases of tuberculosis in Los Angeles County (excluding the municipalities of Pasadena and Long Beach) to the Los Angeles County Tuberculosis Control Registry. We prospectively identified 526 consecutive, confirmed cases of active tuberculosis reported between April and September 1993, excluding children, prisoners, and persons who had died. Also excluded were persons who could not speak one of five common languages in our study population: English, Spanish, Mandarin, Tagalog, or Vietnamese.

Data Collection

We sent potential respondents a letter describing our study and providing them with a phone number to call if they did not wish to participate. Trained bilingual interviewers called all eligible patients using the phone numbers provided by the registry, clinics, directory assistance, or friends or relatives listed in medical records. Because telephone surveys miss homeless persons, interviews were conducted in person at soup kitchens, shelters, and a specialized county clinic for the homeless. Interviewers made an average of 16 attempts to contact respondents. We abstracted demographic and clinical information—radiographic and microbiologic results—from the registry.

After giving informed consent, subjects responded in their preferred language. Interviewers used a structured, symptom-based form to elicit ethnicity, country of birth, length of time in the United States, reason for seeking care, legal status, English proficiency, the language spoken by their health care professional, number of possibly exposed contacts, symptoms, and delay in seeking care. Items were derived from previously validated instruments.[5-8] Researchers then conducted a series of focus groups of tuberculosis patients, evaluating and modifying each item for face and content validity. The translated form for each study language was developed from the English original using back-translation techniques.

The survey instrument defined tuberculosis symptoms as one or more of the following occurring in the previous two years and lasting two weeks or more: cough, hemoptysis, fatigue, fever, weight loss, swollen glands, diarrhea, anorexia, night sweats, pleuritic pain, or lymphadenopathy. Contacts with possible exposure to tuberculosis were persons living in the respondent's household or working in the same room for more than an hour each day.

Fear of immigration authorities was assessed by asking, "Were you afraid going to the doctor might cause trouble with the immigration authorities?" We chose to word the question this way because focus group and pilot data indicated that although subjects understood this to mean possible deportation, specifically mentioning deportation resulted in high rates of missing data.

Data Analysis

Previous research has shown that domestic contacts with exposure to active cases for more than 60 days often show signs of infection.[9] We classified each symptomatic respondent into two groups: those who delayed more than 60 days from the onset of symptoms to first contact with the medical care system, and those who delayed 60 days or less. For the analysis of delay, serious symptoms were defined as cough, hemoptysis, fever, or night sweats. χ^2 Tests and logistic regression techniques from the SAS statistical package were used to examine the associations between characteristics and a delay of more than 60 days in seeking care.[10] Analyzing delay using a continuous outcome measure and nonparametric comparisons did not change the direction or statistical significance of the bivariate results.

To check the reliability of the interview data and to ensure quality control, the principal investigator (S.A.) or project managers (Lorraine Chun, MPH, or Mike

TABLE 1.—*Demographic, Clinical, and Immigration-Related Characteristics of the Study Population*

Variable	*Respondents, No.*	*(%)*
Demographic		
Male	195	(62)
Median age, yr	41	
Ethnicity		
Latino	152	(48)
Asian	72	(26)
African American	38	(12)
White	32	(11)
Other	7	(2)
Clinical		
Abnormal radiograph	271	(88)
Abnormal x-ray film and/or positive TB culture	305	(97)
Cavitary lesion	62	(21)
Positive AFB smear	164	(55)
Any TB symptom lasting 2 weeks or more	248	(79)
Mean no. of exposed contacts	10	
Immigration		
Foreign born	215	(69)
Arrived in US as an adult	182	(60)
Not native English speaker	193	(75)
Poor English ability by self-report	78	(25)
Provider did not speak subject's language*	79	(32)
Language problem in seeking care*	29	(13)
No documents	48	(20)
Feared immigration authorities*	15	(6)

AFB = acid-fast bacilli, TB = tuberculosis

* Only asked of 248 symptomatic patients.

TABLE 2.—*Reasons Patients With Tuberculosis (TB) Sought Care**

Reason	Respondents, No.	(%)
TB symptom	161	(53)
Other symptom	55	(18)
Non-TB medical condition	47	(15)
Screening high-risk groups	31	(10)
Contact training	4	(1)
Other reasons	10	(4)

* Percentages do not add up to 100% due to rounding.

Wada, MD) readministered the instrument to 23 subjects during the data collection process and found only rare inconsistencies. We also compared registry and interview values for variables that could be derived from both sources—age, sex, ethnicity, length of time in the United States, and country of birth—and found good agreement.

Results

Of the 526 identified cases, we were able to contact 365. A total of 313 completed the interview for an overall response rate of 60%. Registry information showed no significant differences between respondents and nonrespondents by age, ethnicity, sex, the proportion born abroad, or radiographic or microbiologic results. A total of 95 different offices, laboratories, agencies, and hospitals reported active cases during the study time period.

Table 1 summarizes the composition of the study group. Subjects were predominantly men. Latino and Asian were the largest ethnic groups. Virtually all subjects had abnormal radiographs or cultures indicating infectiousness. Many had abnormalities indicative of even greater infectiousness: cavitary lesions (21%) or acid-fast bacilli on sputum smear (55%). Subjects possibly exposed an average of ten domestic or workplace contacts.

Immigrants made up more than two thirds of the subjects. Of the immigrants, 85% (60% of total population) arrived in the United States as adults and thus were probably less well acculturated than immigrants who arrived as children. Many patients reported language difficulties: three fourths said they preferred a language other than English, a fourth rated their English ability as poor, a third did not speak the same language as their physician, and one in ten symptomatic patients said that language problems deterred them from seeking care. Of the 255 (71%) patients who responded to the question ascertaining legal status, more than a fifth said they had no immigration documents allowing them to reside in the United States. Only 6% of symptomatic patients felt that fear of immigration authorities had delayed their care.

The preponderance of patients (71%) reported that physicians discovered their tuberculosis when they sought care for a symptom (Table 2). Another 15% were diagnosed in the course of seeking care for another medical condition. Only one in ten said they had participated in screening programs, and only four patients (1%) reported that public health authorities had identified them as contacts of infected patients.

A total of 248 patients had tuberculosis symptoms and are included in the analysis of delay. Only 20% of the study group of patients with active tuberculosis delayed more than 60 days, a period of time that has been shown to result in signs of infection in exposed contacts. Table 3 shows the proportion of patients who delayed more than 60 days by demographic, clinical, and immigration variables. Asians tended to delay longer, as did those who cited language problems, although these trends were not statistically significant. More than 47% of those who cited fear of immigration authorities delayed more than 60 days, as compared with 18% of those who did not cite fear (P = .007). Respondents who feared immigration authorities were almost four times as likely (odds ratio 3.89; 95% confidence interval 1.34 to 11.36) to delay seeking care. This association persisted after adjusting for age, the presence of a serious symptom, cavitary lesion, and positive smear.

Discussion

Many variables associated with recent immigration are common in patients with tuberculosis, although in Los Angeles County in 1993, few patients feared that seeking care would result in difficulties with immigration authorities. Many undocumented patients may be aware that most health care professionals do not report information on legal status to the Immigration and Naturalization Service. Indeed, since the late 1980s,

TABLE 3.—*Associations With Delay in Seeking Care for Tuberculosis-Related Symptoms*

Variable	Delayed >60 Days, No.	(%)	Delayed ≤60 Days No.	(%)
Overall	49	(20)	199	(80)
Demographic				
Age <65 yr	43	(21)	161	(79)
Male	26	(17)	176	(83)
Ethnicity				
Latino	22	(17)	106	(83)
Asian	13	(29)	32	(76)
White	3	(13)	21	(87)
African American	5	(17)	24	(83)
Clinical				
Serious symptoms	12	(14)	71	(86)
Cavitary lesion on radiograph	13	(27)	35	(73)
Positive AFB smear	24	(22)	85	(78)
Immigration				
Foreign born	34	(20)	135	(80)
Arrived in US as an adult	29	(23)	99	(77)
Poor English ability	12	(20)	50	(80)
Language problem in seeking care	7	(25)	20	(75)
No documents	8	(19)	34	(81)
Feared immigration authorities	7	(47)	8	(53)
Did not fear immigration authorities	40	(17)	178	(83)

AFB = acid-fast bacilli, TB = tuberculosis

* Only asked of 248 symptomatic patients

many states have enacted regulations that prohibit sharing information on the legal status of state-funded patients for the purposes of deportation.[11-13]

Our data also indicate that most patients with tuberculosis come to attention because they seek care for symptoms or another nontuberculous medical condition. Most of the symptoms such as cough, fatigue, and weight loss would not require emergent treatment. Comparatively few patients with active disease were found through screening programs or contact tracing. Even if legislation restricting access of undocumented immigrants to health services allowed for emergent treatment and population-based preventive services, the diagnosis and treatment of many patients with active tuberculosis would nonetheless be affected.

Although it was uncommon, fear of immigration authorities was the cultural variable most closely associated with symptomatic patients delaying care. This association was independent of previously shown adjustors for infectiousness and severity: age, symptoms, and radiographic and microbiologic results.[14] Any increase in the fear of immigration authorities that patients experience when seeking medical care is likely to increase the delay between onset of symptoms and first contact with the medical care system. Because each patient possibly exposes an average of ten contacts to the disease during the course of delaying care, such an increase would spread tuberculosis beyond those who delay.

Our study suffers from several limitations. Like all studies of delay in seeking care,[15,16] our survey cannot evaluate the barriers to access faced by patients who never saw a physician. The chronic, symptomatic, progressive nature of the disease should eventually result in physician contact and minimize this bias, however. Moreover, concerns about the proposed legislation would persist because any residual bias would underestimate the prevalence of the fear of immigration authorities and its effect on delay in seeking care. Our study may also suffer from the limitations of the accuracy of self-reported data. The overall response rate was 60%, which may lead to a response bias. Respondents and nonrespondents did not differ on clinical or demographic variables available from the tuberculosis registry, however, and this level of response is common in studies of indigent populations.[17] About 30% of respondents declined to give their legal status. Because those who refused were presumably more likely to lack legal papers, the data provide a minimum estimate of the proportion of undocumented immigrants with active tuberculosis susceptible to a fear of immigration authorities.

To our knowledge, this is the first survey of patients with tuberculosis that examines the relationship of immigration and delay in seeking care. The broad registry-based sampling technique should ensure a study group that can be generalized to other areas with a large proportion of cases of tuberculosis in immigrants. If future research confirms our findings, any policies that increase undocumented immigrants' fear that health care professionals will report them to immigration authorities may exacerbate the current tuberculosis epidemic.

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Article

Fecal Occult Blood Testing for Colorectal Cancer in an Ethnically Diverse Population

GARY A. GLOBER, MD, *Houston, Texas*; SCOTT HUNDAHL, MD; JUDY STUCKE, RN; *and* MARYANN CHOY, MS, *Honolulu, Hawaii*

Fecal occult blood test kits were distributed throughout the ethnically diverse Hawaiian Islands during a 3-week period in 1989. Occult blood was detected in 1,631 persons (11.8%). At least 83% of the participants with positive tests sought medical advice. Subsequently, 76 (4.7%) were diagnosed as having colorectal adenomas and an additional 1.4% had malignant neoplasms (3 gastric and 20 colorectal adenocarcinomas). Three quarters of the colorectal cancers were localized and node-negative. Participation in this program and the type of diagnostic studies done on participants with positive tests varied according to sex and ethnicity. Therefore, these demographic variables must be considered in designing fecal occult blood screening programs.

(Glober GA, Hundahl S, Stucke J, Choy M: Fecal occult blood testing for colorectal cancer in an ethnically diverse population. West J Med 1994; 161:377-382)

Colorectal cancer is the second leading cause of cancer deaths in the United States.[1] The American Cancer Society currently recommends annual digital rectal examinations for all asymptomatic, average-risk subjects aged 40 and older, annual fecal occult blood testing (FOBT), and sigmoidoscopy every three to five years after two normal sigmoidoscopies a year apart beginning at age 50.[2] To be effective, however, any screening program must be financially, physically, and psychologically acceptable to all segments of the populations at risk. Fecal occult blood testing is the cheapest and easiest of all examinations to do, but questions remain about the best ways to convince patients to do the test, to seek a physician if the test is positive, and then to complete the necessary diagnostic evaluations. Critical variables such as age, sex, race or ethnicity, and knowledge about the test influence each of these steps. Although the literature on FOBT is voluminous, investigations to date have not focused on ethnicity. Accordingly, the Queen's Medical Center Cancer Institute (Honolulu) and the Hawaii Division of the American Cancer Society, in conjunction with SmithKline Diagnostics and Pay 'N' Save Stores, sponsored free statewide FOBT screening as a public service in Hawaii's ethnically varied population.

Subjects and Methods

Information concerning the screening program was disseminated through an 11-part series on a local television news program, promotional spots on that channel, a feature article in the evening paper, printed advertisements, and by public service announcements on radio stations. Fecal occult blood testing was offered to anyone who chose to participate. The media campaign stressed that the incidence of colorectal cancer increases with age, and in the absence of risk factors, colorectal cancer is most prevalent after age 50. The American Cancer Society recommendations for annual FOBT to begin at age 50 were stressed. Hemoccult II kits (SmithKline Diagnostics) were available at all branches of a local pharmacy chain (Pay 'N' Save Drug Stores) during a three-week period from June 26 to July 14, 1989. On those islands without participating pharmacies, a public health nursing office and a hospital pharmacy made FOBT packets available. A few kits were mailed to shut-ins on request.

Instructions for the test were made available in four ways: an instruction sheet given out with each kit, pharmacists available at each pharmacy to answer questions, television news spots, and a "hot line" staffed by health professionals and American Cancer Society volunteers. SmithKline Diagnostics provided training for all the professionals and volunteers involved in the program. Participants were advised to avoid red meat, raw fish, peroxidase-containing foods (such as horseradish or turnips), aspirin, anti-inflammatory drugs, vitamin C, and oral iron supplements for two days before testing and during the test period. The instructions directed participants, after collecting two specimens from three consecutive stools (a total of six specimens), to promptly return the kits to the pharmacy or mail them to the Queen's Medical Center.

From the Department of Gastrointestinal Medical Oncology and Digestive Diseases, Division of Medicine, University of Texas M D Anderson Cancer Center, Houston, Texas (Dr Glober), and Queen's Medical Center, Honolulu, Hawaii (Dr Hundahl, Ms Stucke, and Ms Choy).

Reprint requests to Gary A. Glober, MD, University of Texas M D Anderson Cancer Center, 1515 Holcombe Blvd, Box 78, Houston, TX 77030.

Figure 1.—The percentage of male and female sex by age is shown for participants in a fecal occult blood screening in Hawaii (n=15,015).

Returned kits were analyzed by licensed medical technologists after rigorous quality control training by SmithKline Diagnostics. The slides were not rehydrated, but were developed using a stable solution of hydrogen peroxide and denatured alcohol. All properly prepared kits were tested, but any slides that were received more than 12 days after collection were considered invalid if read negative. Slides were also invalid if there was either too much or too little specimen. If any of the smears tested positive, the entire FOBT was considered positive.

All participants were informed of their test results in writing. Letters to those with a negative FOBT stressed that the results did not exclude the possibility of cancer, and the person was urged to seek medical attention if he or she noted any blood in the stool or any change in bowel habits. They were also urged to follow their physicians' colorectal cancer screening advice. If the test was invalid, a letter was sent with an explanation, and another FOBT was recommended. All persons with positive occult blood tests received letters urging them to see their physician so that the exact cause of the occult blood could be determined.

TABLE 1.—*Follow-up Response of Participants With Positive Fecal Occult Blood Test (FOBT)*

Response	*Participants With Positive FOBT* No.	%
Physician's response		
Known method of diagnostic evaluations	809	49.6
Unknown method of diagnostic evaluations	428	26.2
No diagnostic evaluations	78	4.8
Participant refused diagnostic evaluation	41	2.5
No physician or participant response	275	16.9
Total positive FOBT	1,631	100.0

Participants without a physician were encouraged to contact the Hawaii Medical Association for a physician referral list. The finding of a positive test also generated a letter to the physician listed on a person's registration card, plus a form for the physician to document the diagnostic tests performed and the final diagnosis.

Telephone directories for all the islands were checked in an attempt to locate subjects whose letters were returned because of an incorrect or insufficient address, and their physician (if name available) was contacted for a new address. If these attempts were unsuccessful, voter registration lists were checked.

At nine months, a second letter was sent to all persons with a positive FOBT whose diagnostic studies or results remained unknown. This letter gave preliminary results of the screening program and encouraged the recipient to seek medical attention. All physicians who had only one patient requiring follow-up were sent a second letter and form. The rest were contacted by phone.

The χ^2 test was used to make statistical judgments of significance. The null hypothesis was rejected at $P < .05$.

Results

Of 43,433 kits distributed, 15,015 (34.6%) were returned. A total of 1,201 kits (8%) were considered invalid. Although kits were distributed on request to persons of any age, the participation of persons younger than the American Cancer Society recommendations of 50 years, in the absence of risk factors, was not encouraged during the publicity campaign. Occult blood was detected in 1,631 (11.8%) of the valid kits. Of those with a positive FOBT, 83% were known to have sought medical evaluation (Table 1).

Of the 1,631 with a positive FOBT, 23 (1.4%) were found to have malignant neoplasia (Table 2): 3 patients with gastric adenocarcinomas (0.2%) and 20 patients with colorectal cancer (1.2%). Localized, node-negative colorectal adenocarcinomas were detected in 75% (Table 3). Table 4 indicates the percentages of patients with colorectal neoplasia by ethnicity. Of the 20 patients found to have colorectal adenocarcinomas, 4 (20%) had only one FOBT-positive specimen (of the 6 submitted) and 8 (40%) had two or fewer.

Among the FOBT-positive participants, 105 (6.5%) were found to have colorectal polyps—76 adenomatous polyps, 16 hyperplastic, and 13 unspecified (Table 2). The mean age of patients with colorectal cancer was 63.8 years, and of those with adenomatous polyps, 61.1 years.

Figure 1 shows the distribution of age and sex among the 15,015 people returning kits. The mean age was 54 years, and a female predominance was noted ($P < .02$). The youngest participant found to have colorectal cancer was 37, and the youngest participant with an adenomatous polyp was 34.

In Figure 2, the ethnic distribution of participants older than 50 is compared with those of Hawaii residents older than 50 and of persons found to have colorectal cancer and adenomatous polyps. Japanese, white, and Chinese residents participated by sending in the FOBT

TABLE 2.—*Diagnosis in Participants With Positive Fecal Occult Blood Test (FOBT) (n=1,631)*

Diagnosis	Participants With Positive FOBT No.	(%)	Patients With Known Methods of Diagnostic Evaluation (n=809) %
Known neoplastic lesions			
Colorectal cancer	20	(1.2)	2.5
Gastric cancer	3	(0.2)	0.4
Adenomatous polyp	76	(4.7)	9.4
Known nonneoplastic lesions as the sole diagnosis			
Hyperplastic polyp	16	(1.0)	2.0
Unspecified polyp	13	(0.8)	1.6
Hemorrhoids	148	(9.1)	18.3
Diverticulosis	92	(5.6)	11.4
Upper gastrointestinal disease	33	(2.0)	4.1
Chronic inflammatory bowel disease	14	(0.8)	1.7
Miscellaneous	17	(1.0)	2.1
No disease found	377	(23.1)	46.6
Totals	809	(49.5)	100.1

to a greater degree than would be predicted by their relative proportions in the population and Filipinos and Hawaiians to a somewhat lesser degree than would be expected by their percentages of the population.

The diagnostic procedures used to evaluate the presence of a positive FOBT are summarized in Table 5. Of those on whom diagnostic information is available, 33% had only a second FOBT. Information concerning the rationale for merely repeating the FOBT was not solicited from the physicians. As indicated in Figure 3, there were ethnic differences in the methods of evaluation.

Each kit included four questions (Table 6), but differences in answers between those with a positive FOBT and participants with a negative FOBT were not significant. A quarter of those with colon cancer had a family history of colorectal neoplasia. Participants who had either taken or heard of FOBT previously were more likely to have a negative FOBT. Of note, 44% of the participants ultimately diagnosed as having colorectal cancer had heard of the test, but only 19% had been previously tested. There were no significant age, sex, or ethnic differences in the questionnaire responses.

Discussion

The first stage in successful screening programs is influencing people to participate. The television station estimated that 30,862 households watched its evening news programs. If we assume there are two adults per

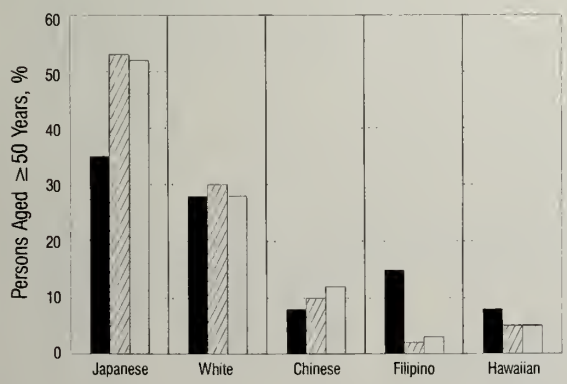

Figure 2.—The ethnic distribution of Hawaii residents (1990) aged 50 years and older (■) is compared with those of study participants aged 50 years and older (▨) and participants aged 50 years and older with a positive fecal occult blood test (⊡)

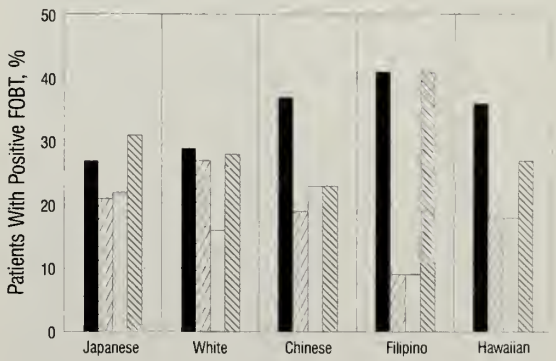

Figure 3.—Methods of diagnostic evaluation are shown by ethnicity. ■ = fecal occult blood test (FOBT) only, ▨ = colonoscopy only, ⊡ = combination of barium enema and either sigmoidoscopy or proctoscopy, ⧅ = miscellaneous (such as barium enema alone, sigmoidoscopy alone, upper gastrointestinal series, gastroscopy)

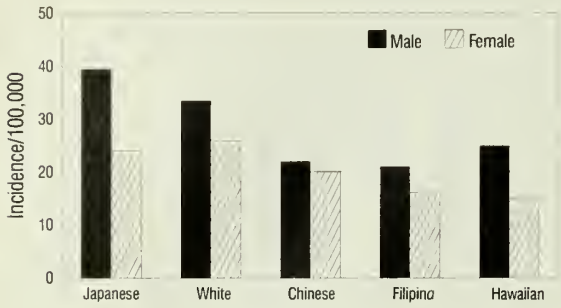

Figure 4.—Age-adjusted incidence is shown for colon cancer in Hawaii, 1983 to 1986, by ethnicity.

house, well over half of the predicted viewers appear to have responded, as 43,433 FOBT kits were taken from the pharmacies. Of those kits, 15,015 (34.6%) were returned. Compliance rates from other studies using a television station for public education and a pharmacy chain for distribution ranged from 20% to 63%.[4-11]

What variables influenced the compliance? We noted a predominance of women who sent in kits (Figure 1)—similar to the finding in studies from New York and Pennsylvania.[4,8] A project in Kansas showed no male-female difference.[5] As for previous experience with the test, 52% of our participants had heard of FOBT before the project, but only 29% had been tested before. In the New York study with a return figure of 20%, 30% had a previous FOBT, but a greater percentage than in our study (79% versus 52%) had previous knowledge of the test.[4] In an earlier program in New York, investigators noted a higher response rate (44%) when participants were required to pay a dollar for the kit.[11] Similarly, Winchester and colleagues found that a "nominal" fee increased the response.[10]

Japanese, whites, and Chinese returned the kits more often than expected from their relative percentage in the population (Figure 2), with the Japanese having the highest participation rate. In a Hawaii-based longitudinal investigation of heart disease and cancer in Japanese men (ages 63 to 72), 92% returned the test.[12] In our project, Filipinos and Hawaiians had a compliance rate somewhat less than expected from their relative rank in the state census. No specific age, sex, or ethnic groups were more likely to send in an invalid kit.

We were not able to quantitate the demographic variables of those who picked up the FOBT kits but did not return them. An analysis of the pharmacy locations and the participants' zip codes indicated that the stores were equally accessible to all races. In Hawaii, there are ethnic differences in the incidence of colorectal cancer (Figure 4) (Mark Goodman, PhD, and Hawaii Tumor Registrar staff, oral communication, March 1991). Perhaps the Filipinos and Hawaiians did not perceive the value of FOBT, given their relatively lower risks. But this would not explain the high Chinese compliance rate.

The next important phase in any screening endeavor is for participants with a positive test to contact their physicians. At least 83% were known to have seen a physician for follow-up, which is comparable to the 73% to 93% found in the other television-pharmacy studies.[4-11] Of course, the remaining 17% may have been examined, but they and their physicians did not respond to our queries. There were no significant differences in age, sex, or ethnicity between those who were known to have sought medical advice and the nonresponders. Neither a knowledge of FOBT nor previous testing influenced whether a person sought a physician's advice for a positive FOBT.

About 12% of the returned kits were positive for occult blood, a higher figure than expected from the yields of 2% to 4% in the other television-pharmacy studies.[4-11] Because of the subjective nature of color-coded results, it is difficult to compare reports in the literature. Perhaps, despite rigorous quality control, our medical technologists "over-read" the tests. The prevalences of diagnoses and the percentage of persons without any

TABLE 3.—*Age, Sex, and Ethnicity of 20 Patients With Colorectal Cancer Detected*

Patient	Age, yr	Sex	Race or Ethnicity	Dukes' Stage*
1	61	M	White	Carcinoma in situ
2	66	M	Japanese	Carcinoma in situ
3	52	M	White	Carcinoma in situ
4	72	F	White	Carcinoma in situ
5	67	F	Japanese	Carcinoma in situ
6	68	F	Japanese	Carcinoma in situ
7	74	F	Japanese	A
8	37	M	Japanese	A
9	68	F	Japanese	B
10	67	F	White	B
11	71	F	Japanese	B
12	60	M	Japanese	B
13	76	M	Part Hawaiian	B
14	62	M	Japanese	B
15	52	M	Japanese	B
16	73	M	Japanese	C
17	70	F	White	C
18	62	M	Japanese	C
19	58	M	Japanese	C
20	60	F	White	D

*Astler/Coller staging system.[3]

TABLE 4.—*Percentage of Patients With Colonic Neoplasia by Ethnicity*

Ethnicity	Patients With Colorectal Cancer		Patients With Adenomatous Polyps	
	No.	(%)	No.	(%)
Japanese	13	(65)	51	(67)
White	6	(30)	17	(22)
Chinese	--		3	(4)
Filipino	--		2	(3)
Hawaiian	1	(5)	3	(4)
Total	20	(100)	76	(100)

TABLE 5.—*Known Method of Diagnostic Procedures to Evaluate Positive Fecal Occult Blood Test (FOBT)*

Diagnostic Test	Participants With Positive FOBT No.	Diagnostic Procedures %
Repeat FOBT only	269	33.2
Colonoscopy only	170	21.0
Barium enema and either sigmoidoscopy or proctoscopy	143	17.7
Barium enema only	42	5.2
Flexible sigmoidoscopy only	26	3.2
Proctoscopy only	20	2.5
Miscellaneous*	139	17.2
Total	809	100.0

*Upper gastrointestinal barium radiograms, gastroscopy, anoscopy.

obvious disease were similar to those of the other investigations.

The final step in the screening process is diagnosing the source of the occult blood. Because lesions can bleed intermittently,[13] a workup should be instituted even if only one stool specimen contains blood. In our series, 33% of those with known diagnostic evaluations had only a second FOBT series done, compared with 12% and 20% in other investigations.[5,7] There were no sex differences, but the Chinese, Filipinos, and Hawaiians were more likely to have only the FOBT repeated.

Because of the substantial risk of neoplastic colorectal lesions in the developed world, a consensus of investigators advises either total colonoscopy or sigmoidoscopy plus an air-contrast barium enema study as the minimum evaluation for a positive FOBT.[14,15] All patients with positive occult blood tests need to be evaluated, even if asymptomatic. Rigid sigmoidoscopy alone would identify only 25% to 33% of cases of colorectal cancer now, compared with more than 50% at the turn of the century.[16] Colonoscopy is the single most effective diagnostic strategy.[17] The value of gastroscopy in a patient with a positive FOBT and a normal diagnostic evaluation of the large intestine is controversial.[18] In our series, three cases of gastric malignancy were detected.

Of those screened who had a positive FOBT and known endoscopic or radiographic evaluations, 21% had at least a colonoscopy and 18% had only a sigmoidoscopy or proctoscopy plus a barium enema. Thus, 61% did not receive appropriate diagnostic tests directed to the large bowel. McGarrity and colleagues found that 39% of participants with positive FOBTs who went to a physician did not have correct examinations.[7] Disappointingly, they were unsuccessful in increasing the number of appropriate colonic tests during a second screening program by mailing physicians a suggested diagnostic algorithm.[8]

TABLE 6.—*Responses to Questions Related to Participant Characteristics*

Participant Characteristic	Answered "Yes" to Question, %* 1	2	3	4
Positive FOBT	16	8	38	19
Negative FOBT	17	6	44	25
Presence of colorectal cancer	24	25	44	19

FOBT = fecal occult blood test

*The questions were as follows:
1. Has anyone in your family had colorectal cancer or polyps?
2. Have you noticed recent changes in your bowel habits?
3. Have you ever heard of the Hemoccult test?
4. Have you ever previously done the Hemoccult test?

In our study, men were more likely (2.5:1) than women to have a colonoscopy, but no sex differences for barium enema plus either sigmoidoscopy or proctoscopy were noted. As expected, subjects younger than 40 years were more likely to have only a repeated FOBT, and there was an increasing percentage of diagnostic evaluations with age up to 75 years. Of all ethnic groups (Figure 3), the Filipinos were the least likely to undergo diagnostic procedures directed to the colon. Having a family history, a change in bowel habits, or previous experience with FOBT did not influence the type of diagnostic procedures used.

Although the concept of Hemoccult blood screening was first introduced in 1971,[19] the value of the FOBT in saving lives was controversial at the time of our study. The dilemma for physicians was whether fecal occult blood testing was worth the effort, cost, and risk involved in evaluating a positive result. Five large prospective trials are currently in progress to give us guidance.[20-24] Preliminary data indicate a positive FOBT rate of 1.1% to 2.4%, positive predictive values for adenoma at 29% to 41%, and positive predictive results for colorectal cancer of 8% to 17%. More important, there was an increased yield of the more favorable Dukes' A and Dukes' B lesions (65% to 78%) compared with 33% to 35% in the controls. The tendency of screening, however, is to have lead and length biases that might erroneously indicate an improved survival and to identify cancers with a more benign potential.[25] We found that 75% of the colon cancers were either in situ, Dukes' A, or Dukes' B, a desirable result indeed. In an earlier Hawaii-based program, the yield of Dukes' A or B lesions was increased from 35% to 59% by screening FOBT and sigmoidoscopy.[26]

Since our Hawaii-based study, a case-control study has been done that suggests that FOBT can lower colorectal cancer mortality.[27] In the most definitive (randomized, prospectively controlled) study published to date, annual FOBT reduced colorectal cancer mortality by 33%.[28] Unlike our project, most of the slides in that study were rehydrated, which increased the positivity rates from 2.4% to 9.8% and the sensitivity from 80.8% to 92.2%, but also increased the false-positive rate.[28]

Attention to the variables that increase the potential for false-positive and false-negative guaiac tests should improve the positive predictive value of these examinations.[29] Newer tests, such as identifying monoclonal antibodies directed against human hemoglobin, might improve the results of fecal occult blood testing.[30] The

most exciting prospect to date involves the testing of biologic materials for oncogene abnormalities—the detection of mutated *ras* oncogenes in feces, for example.[31] Even with the most elegant technologic advances, the reality is that both the lay and professional communities must be motivated to perform screening tests and act appropriately on the results of those examinations. It is hoped that behavioral studies that include variables such as age, sex, and ethnicity will enhance the success rate of cancer prevention and control endeavors.

Summary

A total of 15,015 residents of Hawaii participated in a fecal occult blood testing program designed to screen for colorectal cancer. Of these, 11% tested positive for fecal occult blood, including 1.2% with colorectal cancer, 4.7% with adenomatous polyps, and 0.2% with stomach cancer. Three quarters of the cancers detected were the more favorable, localized, node-negative tumors. Analysis of results from this study suggests noteworthy ethnic variations in both the initial participation and subsequent diagnostic evaluations.

Acknowledgments

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Articles

Community-Acquired Pneumonia in Adults

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Although the frequency of community-acquired pneumonia caused by *Streptococcus pneumoniae* continues to be high, studies show that *Mycoplasma pneumoniae, Chlamydia pneumoniae,* or *Legionella pneumophila* are the etiologic agents in 20% to 40% of community-acquired pneumonia in adults. The clinical presentation of pneumonia caused by these organisms may be indistinguishable from pneumonia due to *S pneumoniae.* Separation of cases of pneumonia due to *S pneumoniae* as typical and that caused by *M pneumoniae, C pneumoniae,* or *L pneumophila* as atypical is unwarranted and unhelpful in planning therapy. As many as 35% to 50% of patients do not have an etiologic agent identified. Community-acquired pneumonia can have high morbidity and mortality in patients who are older, have underlying lung disease, diabetes mellitus, or other comorbid conditions, or who have decreased immune function regardless of the specific etiologic agent. In choosing appropriate empiric antimicrobial therapy in hosts who are not immunocompromised, erythromycin and other macrolide antibiotics have the advantage of being effective against a wide range of pathogens likely to be encountered, including *S pneumoniae, M pneumoniae,* and *L pneumophila,* and of having some benefit against *C pneumoniae.* In other patients, the selection of antibiotic therapy can be based on age, clinical suspicion, epidemiologic data, and laboratory test results. Antimicrobial therapy can be directed at specific organisms when and if they are identified.

(Sue DY: Community-acquired pneumonia in adults. West J Med 1994; 161:383-389)

Pneumonia continues to be a common respiratory tract disease affecting all age groups.[1-3] Despite the recent emphasis on the increasing frequency of tuberculosis, the importance of pneumonia in immunocompromised patients, and the high morbidity and mortality of hospital-acquired nosocomial pneumonia, community-acquired pneumonia remains an important problem both in patients who are otherwise healthy and in those who have underlying long-term respiratory or other diseases. The presence of newly described pathogens, a better understanding of the clinical presentation of pneumonia, new diagnostic methods, and changes in treatment recommendations make community-acquired pneumonia a continually evolving topic.[1-3] In particular, it is now apparent that clinical presentations of pneumonia due to *Streptococcus pneumoniae* and pneumonias caused by *Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella pneumophila,* viruses, or other agents cannot always be distinguished.[1] This finding casts doubt on a physician's ability to separate "typical" pneumonia from "atypical" pneumonia and thereby reliably use clinical features to guide the choice of diagnostic tests and initial therapy.

Pathogens and Epidemiology of Community-Acquired Pneumonia

In retrospective reviews, the precise agent responsible for pneumonia is unknown or uncertain in as many as 50% of patients, even with appropriate diagnostic studies.[1,4,5] Because treatment is often started and continued without knowledge of the actual pathogen, an epidemiologic approach may be helpful.

It is generally accepted that the cause of community-acquired pneumonia is different in recent studies compared with earlier studies. The following are possible reasons:

- An increasing proportion of ambulatory patients have some degree of decreased immune function that may be a factor.
- A number of new microorganisms causing pneumonia have been recently described, and methods for identifying these agents have become available in the clinical laboratory.
- Frequent administration of antibiotics early in the course of disease, and before diagnostic studies are obtained, may contribute to a higher proportion of cases of pneumonia that have no identifiable pathogen.

These factors may explain why many types of microorganisms have been implicated in pneumonia and why in a great number of cases an etiologic agent is not identified. In one study of community-acquired pneumonia in adults, about 70% of whom had an underlying medical condition, a definitive or presumptive cause was

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ABBREVIATIONS USED IN TEXT

HIV = human immunodeficiency virus
MIC = minimum inhibitory concentration

found in only 67%.[1] The two most common pathogens identified were *S pneumoniae* (pneumococcus, 15.3%) and *Hemophilus influenzae* (10.9%). Fewer but about an equal number of cases were identified as being caused by *Legionella* species, *C pneumoniae*, and aerobic gram-negative bacilli. *Mycoplasma pneumoniae* was uncommon in this study group, as were viruses, staphylococci, and others. This study group, although representative of adult patients, may have had a high proportion of patients with chronic obstructive pulmonary disease, alcohol abuse, a malignant neoplasm, diabetes mellitus, or other chronic conditions that may alter the types of organisms associated with pneumonia. For example, preexisting disease was seen in as many as 75% of those in whom pneumococcal pneumonia developed as opposed to a much lower frequency of preceding disease in patients with *M pneumoniae*. Furthermore, about a third of the study group was immunocompromised from infection with the human immunodeficiency virus (HIV) or from other causes.

Another series included 154 episodes of community-acquired pneumonia in veterans, of whom only 79 had an etiologic diagnosis.[4] Of these, 13 had *L pneumophila* or *Legionella micdadei*, 12 had gram-negative enteric bacilli, and 8 had *S pneumoniae*. Among others, a diagnosis of pneumonia from *C pneumoniae* was made in 8 patients, and *M pneumoniae* was thought to be the etiologic agent in 3 patients. In another series with fewer patients having underlying diseases, the three agents (other than viruses and tuberculosis) that most often caused nonpneumococcal community-acquired pneumonia were *M pneumoniae*, *Legionella* species, and *C pneumoniae*.[6]

An identified nonviral organism associated with pneumonia and considered to have features different from lobar pneumococcal pneumonia—that is, atypical pneumonia—was *M pneumoniae*, identified and isolated in the 1960s. These organisms are free-living bacteria that lack a cell wall but that can be grown using appropriate culture media. *Mycoplasma pneumoniae* is responsible for 15% to 35% of cases of pneumonia in outpatients, occurring in patients with and without underlying disease. Although usually associated with a healthy younger group of patients who are often confined in close quarters such as a family unit, military base, or dormitory, pneumonia from *M pneumoniae* is an important disease in older persons in whom severe pneumonia requiring a hospital stay may be seen.[7,8]

The epidemic of legionnaires' disease seen in Philadelphia, Pennsylvania, in 1976 triggered an intense effort that resulted in the identification of the responsible pathogen, *Legionella pneumophila*. These aerobic gram-negative bacilli were subsequently found to have been a causative agent in a number of previously undiagnosed cases of pneumonia. Since then, some 20 other *Legionella* species have been associated with pneumonia. These organisms are responsible for both episodic and epidemic outbreaks in the community and in hospitalized patients. Outbreaks have often been associated with contamination of the hot water supply; person-to-person spread does not occur. Among cases of community-acquired pneumonia, *Legionella* species is the causative organism in 1% to 15%, and patients frequently are older and have a history of cigarette smoking.[9,10]

Chlamydia pneumoniae was identified only within the past decade, and the name "TWAR," taken from identification labels of initial laboratory isolates, is still occasionally used.[11,12] *Chlamydia trachomatis* and *Chlamydia psittaci* are the other known species of this genus, which are obligate intracellular organisms that can be seen by using electron microscopy. These organisms use the cellular apparatus of infected cells for energy production and replication. *Chlamydia pneumoniae* is responsible for about 6% to 12% of cases of adult community-acquired pneumonia, sometimes occurring sporadically and sometimes in epidemics.[1,6] Outbreaks among military personnel and college students support the notion that close contact with infected persons is a risk factor. Infection with *C pneumoniae* may be cyclical, with four-year cycles of increased infection rates having been demonstrated from serologic testing.

Gram-negative aerobic bacilli and staphylococci are other bacterial pathogens that cause pneumonia more frequently in certain patient groups. These organisms are infrequent colonizers of the upper respiratory tract in healthy persons, but increase in number in those requiring increasing supportive and medical care. Thus, although in-hospital patients frequently have gram-negative rods found in the oropharynx, as many as 42% of ambulatory patients in a health care facility also may be colonized by these organisms.[13] Pneumonia in nursing home patients, although acquired in the "community," is more often due to these bacteria than may be suspected.

Hemophilus influenzae pneumonia is seen with increased frequency in patients with chronic obstructive pulmonary disease, alcoholism, smoking, and HIV infection. In particular, *H influenzae* type b is most often associated with pneumonia. Although other serotypes and nontypable *Hemophilus* species are more often colonizers or involved with upper respiratory tract infections, these may also cause lower respiratory tract infection. In patients with chronic lung disease and recently in immunocompromised patients, *Moraxella (Branhamella) catarrhalis* has been reported as a cause of pneumonia.

Viruses remain important and are probably underidentified etiologic agents in community-acquired pneumonia. Although adenovirus may infect young adults, especially military recruits, pneumonia due to this agent is usually mild and self-limited. Varicella-zoster virus is associated with severe pneumonia in adults, but diagnosis is usually not a problem. Influenza virus is the most important cause of epidemic viral pneumonia, with

important implications for immunization in the most susceptible populations—older patients and those with long-term disease. Influenza can be mild or severe enough to result in death from respiratory failure; often bacterial superinfection is considered to be a factor. A diagnosis of influenza is usually made in conjunction with a known community spread of influenza virus. Consideration is particularly important because of the possible beneficial response from amantadine hydrochloride if given very early for influenza type A. Cytomegalovirus is an important pathogen in immunocompromised patients, especially those receiving immunosuppression following solid organ and bone marrow transplantation.

Mycobacterium tuberculosis must at least be considered in all patients with community-acquired pneumonia. Although risk factors and clinical presentation are important in assessing the likelihood of mycobacterial infection, tuberculosis in persons heretofore considered "low risk" is reported with increasing frequency. Therefore, any clinical suspicion of tuberculosis should be pursued. In appropriate geographical areas, fungal pneumonia caused by *Coccidioides* and *Histoplasma* organisms are important causes of community-acquired pneumonia.

Tuberculosis, fungal pneumonia—especially endemic mycoses such as *Coccidioides* and *Histoplasma* species, and *Aspergillus* and *Cryptococcus* organisms—and *Pneumocystis carinii* should be considered possible etiologic agents of pneumonia in HIV-infected patients. Although these pathogens are considered highly likely and, therefore, are appropriately sought in those with known HIV infection, patients with undiagnosed HIV may present with infection with one of these organisms.

Community-Acquired Pneumonia—Typical Versus Atypical

In view of the many possible pathogenic organisms responsible for community-acquired pneumonias, it would be important to identify and initiate therapy for the most likely etiologic agents. This concept has long been responsible for dividing community-acquired pneumonias into typical and atypical presentations.

Clinical features of typical pneumonia are often equated with the common clinical presentation of pneumonia caused by *Streptococcus pneumoniae* (pneumococcus). This presentation is characterized by the onset of productive cough with purulent green, yellow, or rust-colored sputum, fever, chills, pleuritic chest pain, leukocytosis, and lobar consolidation on chest radiograph. Patients often have underlying medical problems. Hypotension, mental status changes, lethargy, confusion, and disorientation may be other manifestations. Pneumococcal pneumonia is associated with severe disease and is a leading cause of death in older persons and those with immune systems that are inadequate.

Atypical pneumonia usually consists of the gradual onset of an irritating, nonproductive cough, occasional scanty sputum, myalgias and arthralgias, upper respiratory tract symptoms, and a lack of consolidation on chest radiographs. Patients less often have underlying medical conditions, mental status changes, or hypotension. In the past, atypical pneumonias usually have been associated with *Mycoplasma* species, but more recently *C pneumoniae* and other causes have been found. Although there may be distinguishing features such as hyponatremia, diarrhea, abnormal liver function test results, and high fever in pneumonia caused by *L pneumophila*, these patients are also considered to have features of atypical pneumonia. Atypical pneumonias have generally been regarded as having a milder course and a better outcome.

Studies have shown, however, that the clinical and radiographic features of pneumonia caused by organisms associated with atypical pneumonia are indistinguishable from pneumonia caused by *S pneumoniae* (typical pneumonia). In a study of 359 patients with community-acquired pneumonias, a comparison was done of 55 patients with *S pneumoniae*, 39 with *H influenzae*, 24 with *L pneumophila*, and 22 with *C pneumoniae*, and no significant differences were found between the clinical features or underlying conditions.[1] For example, sputum production occurred in 74% of those with pneumococcus but in 75% of those with *L pneumophila* and 62% of those with *C pneumoniae* as causes of pneumonia. Such features as a "viral-like" prodrome, chills, consolidation, and changes in mental status did not distinguish patients with these disorders. This study was limited in that only five patients were found to have *M pneumoniae*, and they were not included in this comparison. The investigators concluded that pneumonias due to *Chlamydia* and *Legionella* species did not show sufficient atypical features to distinguish them from pneumococcal or *H pneumoniae* pneumonia.

Several studies have not supported the concept that pneumonias caused by the organisms associated with atypical pneumonia are less severe. For example, in one study it was found that the patients with severe community-acquired pneumonia—defined as those requiring admission to hospital for respiratory failure, altered mental status, hypotension, multilobar disease, or pleural effusions—included 7 patients with *L pneumophila* among a total of 67 patients, compared with 11 with pneumococcus.[5] In another report, 64 patients with *M pneumoniae* required admission to a hospital.[7] Clinical features of these patients' illness were indistinguishable from those of other causes of pneumonia. Although none of the patients with *Mycoplasma* pneumonia died, this group made up 5% of the patients with pneumonia who required hospitalization.

Evaluating Cases of Community-Acquired Pneumonia

The evaluation of a case of suspected community-acquired pneumonia is directed at establishing a diagnosis of pneumonia, identifying the etiologic agent, and determining whether or not the patient needs to be admitted to a hospital.

Diagnosing community-acquired pneumonia from the history and the results of a physical examination is

usually not difficult, although some patients will have predominant features of upper respiratory tract symptoms and nonspecific findings on a chest examination. Symptoms suggestive of lower respiratory tract involvement include dyspnea and chest pain, but sputum production may be evidence of bronchitis rather than pneumonia. Although, as emphasized previously, pneumonia due to nonpneumococcal organisms cannot always be distinguished from typical pneumonia, the findings of relative bradycardia with high fever, altered mental status, diarrhea, hypophosphatemia, and renal insufficiency (*L pneumophila*); pharyngitis, bullous myringitis, arthritis, and skin rashes, including erythema multiforme (*M pneumoniae*); or pharyngitis, conjunctivitis, sinusitis, lymphadenopathy, and poor clinical response to erythromycin (*C pneumoniae*) may be helpful. Chills can occur in patients with pneumococcal pneumonia (58%), pneumonia from *L pneumophila* (42%), and pneumonia due to *C pneumoniae* (53%).[1]

A chest radiograph is helpful in confirming the presence of community-acquired pneumonia but may not be needed in every patient. Those at high risk or with immunocompromise, hypoxemia, severe symptoms, serious underlying disease, chronic lung disease, heart failure, or other high risks such as advanced age, as well as all patients in whom hospital admission is considered, should have a radiologic examination initially. In young healthy patients who will be treated as outpatients, a chest radiograph should be taken if there is poor initial response to treatment, a suspicion of immunocompromise, severe symptoms, or other unusual features of disease. The chest radiograph may occasionally be helpful in distinguishing pneumonia caused by *S pneumoniae* from other community-acquired organisms. For example, only small pleural effusions are usually seen with *M pneumoniae*, *L pneumophila*, and *C pneumoniae*; consolidation is unusual with *M pneumoniae* and *C pneumoniae*; and cavitation is rarely if ever a feature of pneumonia caused by the atypical agents, but may be seen with *L pneumophila*. Chest radiographs should be repeated in patients admitted to a hospital to follow the rate of resolution. Radiographs should be correlated with clinical features including fever, arterial blood gas determinations, and other findings. A second chest radiograph to document resolving pneumonia should be done in those patients who have an increased risk for lung cancer—smokers, those older than 40 years, and those with other risk factors—but complete clearance of the infiltrate may take longer than two months in some patients. In those with slow or poor radiographic resolution, further investigation may be indicated for the presence of chronic lung disease or malignancy.

Recently a mortality of 21% (14 patients) was found in a prospective study of 67 patients with severe community-acquired pneumonia, defined as those having respiratory failure, septic shock, extrapulmonary septic complications, altered mental status, multilobar involvement, or cavitation.[5] Of 32 patients with an etiologic diagnosis, 12 (38%) had *S pneumoniae*, 7 (22%) had *L pneumophila*, and 8 (25%) had gram-negative bacilli. Risks for death included advanced age, the presence of other severe disease, and septic shock.

Sputum examination and culture are often insensitive and nonspecific in determining the etiologic agent; therefore, these tests should be done selectively in patients with community-acquired pneumonia. In a recent consensus statement of the American Thoracic Society, the value of the Gram's stain of sputum was questioned because of the lack of studies comparing sputum Gram's stain results and cultures of alveolar material.[3] Although for a healthy young patient, empiric treatment usually is given based solely on a clinical estimate of the most likely cause, a Gram's stain of sputum—but not culture because of its poor sensitivity and specificity—can be helpful in suggesting but not confirming the presence of *S pneumoniae*. In those with chronic lung disease, Gram's stain findings may suggest *H influenzae*. On the other hand, the absence of organisms on Gram's stain supports but does not confirm pneumonia due to *L pneumophila*, *M pneumoniae*, *C pneumoniae*, or virus.

If *L pneumophila* is suspected, direct immunofluorescence of sputum is occasionally positive, but this test is relatively insensitive. The presence of *L pneumophila* antigen in the urine can provide rapid evidence of acute infection, whereas a rise in antibody titer to *L pneumophila* is helpful only for making a retrospective diagnosis. Although serum cold agglutinins may be present in patients with *M pneumoniae* (presumptive diagnosis if present in a titer of 1:64 or higher), these are insensitive and nonspecific; a fourfold rise in complement fixation antibody titer measured during and after the resolution of disease can provide retrospective confirmation of infection. A diagnosis of pneumonia due to *C pneumoniae* can be made from serologic evidence of a rise in immunoglobulin M or G levels against *Chlamydia* species between the acute and convalescent periods.

Blood cultures should be done in all patients admitted to a hospital with pneumonia. In selected patients, especially those with decreased immunity, additional studies may be warranted, including acid-fast stains of sputum and other specimens, mycobacterial and fungal cultures, viral cultures and serologic tests, fiberoptic bronchoscopy, and lung biopsy. Transtracheal aspiration, the insertion of bronchoscopic protected-brush catheters, bronchoalveolar lavage, or needle aspiration of the lung should not be done unless there is a need for a rapid specific diagnosis or a particular indication is present.

The agent causing community-acquired pneumonia may not be confined to the lungs. Infection can extend to the pleural space, resulting in empyema that may require tube or surgical drainage for appropriate resolution. Bacteremia may spread to the meninges—*S pneumoniae*, *H influenzae*, gram-negative bacilli—heart, joints, pericardium, and other locations in both immunocompetent and immunodeficient patients.

Treatment

Fewer than 10% of young healthy patients with pneumonia will be ill enough to require admission to a hospital. The other 90% can be treated successfully as outpatients. Older patients and those with underlying diseases will require hospital care in as many as 80% of cases, however. Considerations for admission to the hospital may include the following[1,3,5,7,14]:

- The need for careful monitoring for the development of signs of respiratory failure or sepsis—underlying lung disease, chronic obstructive lung disease, hypoxemia, multilobar involvement, hypotension, or extreme leukocytosis or leukopenia;
- The need for parenteral antibiotics—respiratory failure, sepsis, pneumonia complicated by abscess or empyema, or an inability to take oral medications;
- Extrapulmonary complications such as meningitis;
- Severe underlying disease or compromise of the immune system—diabetes mellitus, liver disease, heart failure, renal failure, HIV infection, cancer, or corticosteroid use; or a previous need for admission to hospital for community-acquired pneumonia; and
- The presence of predictors of increased mortality or a complicated course—tachypnea, hypotension, the need for vasopressors, extrapulmonary infection, altered mental status, abnormal renal function, cavitation, pleural effusion, anemia, disseminated intravascular coagulation, or coagulopathy.

Patients with severe complications of pneumonia, such as hemodynamic compromise or respiratory failure, are best managed in an intensive care unit. A failure to respond to treatment in a reasonable time—48 to 72 hours as an outpatient—is also an indication for admission to hospital.

The choice of antibiotic for patients with community-acquired pneumonia is made using a combination of clinical suspicion, epidemiologic factors, underlying medical condition, and the results of Gram's staining. The lack of a proven ability to distinguish pneumococcal pneumonia from those organisms associated with atypical pneumonia, plus the recognition of the increased importance of *M pneumoniae*, *L pneumophila*, and *C pneumoniae* in both hospitalized and nonhospitalized patients with pneumonia has led to the choice of erythromycin as empiric therapy for many patients with community-acquired pneumonia. In the earlier-described study of 359 cases, for example, 71% of the etiologic agents identified would likely have been susceptible to erythromycin.[1] Erythromycin is effective against *S pneumoniae* and *L pneumophila* (when 1 gram is given 4 times a day) and is associated with a decreased duration of symptoms in pneumonia caused by *Mycoplasma* and *Chlamydia* organisms. In patients in whom *C pneumoniae* as the cause of pneumonia is strongly suspected, treatment with tetracycline or doxycycline may be preferred over the use of erythromycin, but these antibiotics are less effective against pneumococci and *Legionella* species. Rifampin can be used in conjunction with erythromycin for *L pneumophila*. Clinical experience with the newer macrolide antibiotics, clarithromycin and azithromycin, for the treatment of pneumonia caused by *C pneumoniae*, *M pneumoniae*, and *L pneumophila* is limited.

Although often chosen for the empiric treatment of pneumonia, cephalosporins given alone are not usually the treatment of choice in pneumonia without an identified cause. Second-generation cephalosporins such as cefuroxime are effective against *S pneumoniae*, *H influenzae*, and *M catarrhalis*, but they are not useful in treating *Mycoplasma*, *Chlamydia*, and *Legionella* species. Cephalosporins should generally be reserved for patients with chronic obstructive lung disease, alcoholism, or other conditions that predispose to pneumonia caused by organisms susceptible to these agents. The combination of erythromycin plus a second-generation cephalosporin may be indicated in patients with pneumonia for whom broader antibacterial coverage is needed because of advanced age or underlying comorbid conditions. Of note, the prospective study of 67 patients described earlier found that mortality was 15% (7 of 47 patients) in those with severe community-acquired pneumonia when the initial antibiotic regimen included erythromycin plus tobramycin or cefamandole (second-generation cephalosporin), but of 19 patients who were given other regimens, 6 (32%) died.[5]

A 1993 ad hoc committee of the American Thoracic Society addressed initial empiric antibiotic therapy for community-acquired pneumonia and made similar recommendations.[3] They recommended that outpatients younger than 60 years without other medical problems—including the risk of HIV—be given erythromycin or tetracycline as initial empiric treatment. For these patients, the likelihood that the pneumonia was caused by an organism susceptible to these antibiotics was considered high. For outpatients older than 60 years or who have other medical conditions, it was recommended they be given a second-generation cephalosporin or the combination of trimethoprim and sulfamethoxazole or a β-lactam antibiotic plus β-lactamase inhibitor such as the combinations of ampicillin sodium and sulbactam sodium or amoxicillin and clavulanate potassium, and each of these regimens should have erythromycin added if there is a sufficient suspicion of *L pneumophila*. The recommendations for those with pneumonia severe enough to be admitted to a hospital reflect a greater concern for gram-negative organisms, as second- or third-generation cephalosporins or a β-lactam–β-lactamase inhibitor is recommended with or without erythromycin. In patients admitted to a hospital with community-acquired pneumonia in whom broad empiric coverage is essential, the American Thoracic Society committee recommended both a macrolide (erythromycin) and a third-generation cephalosporin with activity against gram-negative bacilli, especially one with anti-*Pseudomonas* activity, such as ceftazidime.

The duration of treatment with antibiotics depends

on a patient's clinical response; specific recommendations cannot be made. Intravenous antibiotics should be given to patients admitted to hospital with serious disease, especially those with bacteremia, extrapulmonary manifestations, sepsis, respiratory failure, or immunocompromised conditions. If there is an adequate clinical response, including decreased fever and leukocytosis, improvement in the chest radiograph, and resolution of the factors defining severe pneumonia, the regimen can be switched to an appropriate oral antibiotic after three to six days to complete a two- to three-week course. In those treated on an outpatient basis who do not have features of pneumonia that necessitate hospitalization, oral antibiotics can be given for the entire treatment course with careful follow-up to ensure that symptoms resolve appropriately. The total duration of treatment should be tailored to a patient's clinical condition, especially the presence of underlying long-term illness and the capacity of the immune system.

If and when a specific pathogen is identified and the clinical course is consistent with this finding, directed therapy can then be given. Patients with proven *S pneumoniae* pneumonia are almost always treated effectively with intravenous penicillin G or, if clinical manifestations are less severe, oral penicillin V. Despite isolated reports, antibiotic-resistant *S pneumoniae* has been considered rare in the United States. For example, in data reported to the Centers for Disease Control from 1979 to 1987, about 5% to 10% of *S pneumoniae* isolates were resistant to penicillin (minimum inhibitory concentration [MIC] ≥ 0.1 μg per ml) and only 0.3% were resistant to erythromycin,[15] although rates of antibiotic resistance were reported higher in some regions of the country, such as Alaska and the southwestern states. On the other hand, isolates in parts of Europe and in South Africa are frequently resistant to penicillin and other antibiotics, with as many as 50% to 70% of isolates showing relative or high penicillin resistance. Much of the attention to antibiotic-resistant *S pneumoniae* has been focused on meningitis because of the need to achieve antibiotic levels in the cerebrospinal fluid that exceed the increased MIC of the resistant organisms.[16] The importance of antibiotic-resistant *S pneumoniae* in adults with pneumonia remains uncertain. A study in Spain of adults with bacteremic penicillin-resistant *S pneumoniae* pneumonia found an increased association with the presence of underlying diseases (malignancy, liver disease, alcoholism), recent antibiotic use (65% within 3 months), recent hospitalization, an episode of pneumonia within the past year, and greater clinical severity compared with patients with nonpenicillin-resistant *S pneumoniae* infection.[17] Mortality was also significantly higher. In patients with intermediate resistance to penicillin (MIC 0.12 to 2.0 μg per ml), treatment with high-dose penicillin appeared to be successful, but those with more highly resistant organisms responded poorly. The ideal treatment of adults with pneumonia caused by known or suspected antibiotic-resistant *S pneumoniae* has not yet been defined.[16] One approach to *S pneumoniae* pneumonia in the United States would be to look for antibiotic-resistant organisms if there is a high community or hospital prevalence of resistance, if the patient has received antibiotics within the past three months, if pneumonia is clinically severe, or if meningitis is suspected. In these patients, therapy with either higher doses of penicillin (2 to 4 million units every 4 to 6 hours) or vancomycin hydrochloride can be started until susceptibility results become available.[16]

Some strains of *H influenzae* produce β-lactamase, so that second- and third-generation cephalosporins or drugs such as amoxicillin-clavulanate should be given when pneumonia is caused or suspected to be caused by these organisms. β-Lactamase production is commonly found with *M catarrhalis* infection; treatment generally is with amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, or third-generation cephalosporins.

Prevention

Physicians have long been aware of the continued high mortality or severe complications from *S pneumoniae* pneumonia in certain subgroups of patients despite prompt and correct antibiotic therapy. Pneumococcal vaccine, intended to immunize against 23 serotypes of *S pneumoniae*, has been shown to be effective in 50% to 60% of patients in preventing pneumonias caused by these organisms. Moreover, these 23 serotypes include approximately 80% to 85% of the *S pneumoniae* causing severe pneumonia with bacteremia or central nervous system involvement.

Pneumococcal vaccination is currently recommended for all patients older than 65 years and for selected subgroups. These subgroups include patients with some degree of immunosuppression, such as those with functional asplenism, splenectomy, organ transplants, nephrotic syndrome, renal failure, diabetes mellitus, or those receiving cancer chemotherapy. Others who should receive vaccination are patients with chronic congestive heart failure, chronic lung disease, alcoholism, and cirrhosis.

Immunization against other organisms that cause pneumonia is not available. Because pneumonia frequently complicates influenza in older patients and in patients with chronic illness, however, yearly influenza vaccination is also recommended for the prevention of pneumonia.

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Articles

'Pals'
A Medical Student Public Service Program

JUDITH L. SCHAECHTER, MD, *Stanford, California, and* EMILY HARRIS CANNING, MD, *Pittsburgh, Pennsylvania*

We designed a public service and educational program to aid children and families coping with chronic illness and to augment medical student education. Medical students developed relationships with chronically ill children and families based on the Big Brother-Big Sister program model. In addition, students attended bimonthly seminars on childhood chronic illness and family dynamics. Medical students learned about the psychosocial aspects of illness through these relationships and reported that the program contributed to their sense of worth as caregivers. By fostering students' innate altruism, medical schools may succeed in cultivating caring and humanism in their student physicians. We propose a model that encourages medical students to relate personally with patients and their families. A program such as this has the potential to nurture compassion in medical students, contribute to medical education, and provide support to patients and families.

(Schaechter JL, Canning EH: 'Pals'—A medical student public service program. West J Med 1994; 161:390-392)

Altruism has long been considered the primary motivation of students pursuing a medical career. Making a difference in people's lives and serving the community are among the top reasons students give for choosing medicine as a profession.[1] These feelings change during medical education and training. According to several studies, medical students become increasingly cynical during the course of their training.[2,3] Changes in students' attitudes and motives and an increase in the level of symptoms of depression have been reported.[4] Anecdotes suggest that student unhappiness derives from a sense of disillusionment and uselessness.[5] This dissatisfaction may relate to a lack of opportunity to gratify the humanitarian incentives that lead to medical training.

Education is central to the preparation of students for clinical medicine. Humanistic care depends on acquiring skills in treating others with understanding, empathy, dignity, and respect.[6] Little has been published, however, on how medical education influences a student's sense of altruism. Instruction concerning the psychosocial, emotional, and interpersonal aspects of health care is often inadequate,[7,8] and most medical schools continue to emphasize science and the disease process rather than the humanistic aspects of patient care.[3,8] Students often do not see patients during the first two years of training, and this exclusive focus on disease may contribute to a loss of genuine concern for patients.[9] In contrast, students cite early patient contact as one of the most valuable aspects of their medical education and as motivation for further learning.[10]

Studies of public service programs for medical students have focused on the contributions of these programs to the public and not on the benefits to developing physicians. We describe a service program in which medical students interact directly with patients and families during the first years of their training.

"Pals" is a student-initiated public service program that fosters relationships between medical students and chronically ill children or their siblings. The program is a specialized adaptation of the Big Brother-Big Sister program and is modeled after a similar project at Brown University Program in Medicine, Providence, Rhode Island. Medical students and pediatric patients or their siblings are paired as "pals" who visit one another weekly for various activities. In addition, medical students participate in bimonthly seminars on child development, chronic illness, and family dynamics. The program was developed with three main goals: to educate the students; to help the children directly; and to provide support for their families.

We evaluate the program's success in reaching the first goal by involving students in the social, psychological, emotional, and family aspects of the life of a chronically ill child.

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Participants and Methods

While in their preclinical years of training, 11 students volunteered for the first year of the program. The group included 3 men and 8 women. All gave informed consent to participate in the program evaluation.

The students were interviewed three times: before the start of the program, six weeks after meeting their pediatric "pals," and at the completion of the seminar course. The semistructured, open-ended interviews were conducted by one of us (J.L.S). Participants were asked about their thoughts on chronic illness, pain, and death; their understanding of children's ability to cope with adversity; their comfort with chronic illness and death; what they had learned from their experience; what was difficult in the experience; and whether their expectations were met. All students were free to refuse to answer any question and were invited to make additional comments. Interviews were transcribed and reviewed to identify recurrent themes, common experiences, and perceived learning.

Results

Wanting to Make a Contribution

Initially students were asked what they wanted from the relationship with their "pals." Of the 11 students, 6 said that they sought to contribute something meaningful and described the importance of making a contribution in the life of another. The opportunity to be altruistic seemed an important inducement for these students to participate in the program. Similarly, at the closing interview, students spontaneously commented that they had contributed to the well-being of the child and family through their involvement.

Experience of Illness

The program exposed students to the multifaceted aspects of disease for each child and family. Michael was a school-aged boy in remission from cancer. A second child in his family had a disability, and the family had been largely abandoned by friends and relatives after the cancer diagnosis. The medical student, Paul, established relationships with Michael's parents and siblings and spent time with the entire family. Paul came to understand the family's struggles in rearing two chronically ill children and felt that the family appreciated his support and involvement. Paul now plans a career in pediatrics, recognizing more clearly the challenges and rewards of working with ill children.

Another Pals match highlighted the ordeals experienced by a person with cancer. Eric was a terminally ill, angry, and difficult adolescent whom the staff included in the program with some trepidation. Eric rarely attended school, socialized with few peers, and participated in physical activities infrequently. His "pal," David, was an athlete and a gregarious medical student who came to understand a childhood unlike his own. David was pleased with his ability to overcome obstacles to gain Eric's trust.

Failed Matches

Of the student-patient relationships, four were less than successful. Of these students, three of four said they felt they had missed an opportunity to make a contribution in an ill child's life. All of these students continued in the seminars, and one participated in the program the following year. Although disappointed, the students thought they gained an additional perspective about children and their families from listening to the experiences of the other participants.

Discussion

As participants in the program, medical students were able to contribute to a child's and a family's experience while learning about the broader issues associated with chronic illness. The program offered a unique focus on individual and family issues rather than on the disease process.

These students appreciated the opportunity to help others and to express their inherent altruism. Three fourths of the group commented on the importance of giving to others. Our interviews suggest that medical students yearn to be involved in patient care during their preclinical years and lack opportunities to do so. This delay could contribute to the discouragement and demoralization experienced during medical school.

Altruism is thought to be a prime motivator in directing persons into the health care professions. The experience of medical training may deaden motivation by denying students opportunities to express their altruism as years of intense study delay the feedback they seek. Medical students often deteriorate through their professional education from enthusiastic, humanitarian first-year students to tired and disillusioned fourth-year students viewing a profession far removed from the caring vocation they once imagined.[5,12] Medical educators are striving to incorporate ethics and humanitarianism into medical school curriculums, but often this takes the form of lectures and expanded course work. First-hand experience in the psychosocial aspects of medical care might benefit patients and aid in developing humanism in future physicians.

This model enables medical students to relate personally with patients and their families. A program such as this has the potential to nurture compassion in medical students while providing support to patients and their families.

Our study has several limitations. Our sample size is small and composed of self-selected volunteers. In addition, our assessment of the project is not comprehensive or statistically stringent. Rather, we aim to highlight positive aspects of the program and an important and unexpected finding that raises a question of whether medical education adequately supports student altruism or defeats itself in the goal of producing humanistic physicians.

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* * *

GYNECOLOGICAL CHECK-UP

He knows me better than I know myself
having delivered me of two.
I see down to my navel, the white sheet
hiding my parted legs from me.
Slow, smooth, and cool the probe insinuates.
"Beautiful," his voice floats up
from where he crouches on his sibyl's stool.
"Everything's perfect." He comes up smiling.

Years back, when that dead foetus
would not leave my womb,
he did not talk until we sat, I fully clothed,
he in authority behind his desk,
as though my dress
could make that death
respectable.

JEAN HOLLANDER©
Hopewell, New Jersey

Conferences and Reviews

Paradoxes of Body Fluid Volume Regulation in Health and Disease

A Unifying Hypothesis

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The body's normal homeostasis is maintained by the integrity of the excretory capacity of the kidneys. In advanced cardiac failure, however, the avidity of the renal sodium and water retention contributes to the occurrence of pulmonary congestion and peripheral edema. In patients with advanced cirrhosis, the kidneys again fail to excrete the amounts of sodium and water ingested, thus leading to ascites and peripheral edema. The signals for this renal retention of sodium and water in a patient with cirrhosis must be extrarenal because when the same kidneys are transplanted into persons with normal liver function, renal sodium and water retention no longer occurs; rather, the kidneys maintain normal fluid and electrolyte balance. Excessive sodium and water retention by the kidneys also occurs during pregnancy despite a 30% to 50% increase in plasma volume, cardiac output, and glomerular filtration rate. What are the afferent and efferent signals whereby normal kidneys retain sodium and water so that total extracellular, interstitial, and intravascular volumes expand far beyond those limits observed in normal subjects? These dilemmas are the subject of this review, in which a "unifying hypothesis of body fluid volume regulation" is presented.

(Schrier RW, Niederberger M: Paradoxes of body fluid volume regulation in health and disease—A unifying hypothesis. West J Med 1994; 161:393-408)

The regulation of body fluid volume is important in almost every area of medicine and has been the focus of myriad investigations during this century. When most of life was in a saltwater environment and the species' integument was freely permeable to solutes and water, the compositions of the milieu *intérieur* and *extérieur* were comparable. But when the species moved to land, there was the necessity for a sensitive regulatory system for body fluid volume and composition. The importance of this system was perhaps best emphasized by Claude Bernard when he wrote that "the constancy of the milieu *intérieur* is the condition of free and independent existence."[1]

Various studies in this century examining the regulation and composition of body fluid volume have led to many paradoxical observations, some of which we will summarize here. With the loss of gastrointestinal fluid or hemorrhage, a decrease in extracellular fluid, plasma, and blood volume occurs, and the kidneys respond in what would be viewed as an appropriate manner by retaining sodium and water. But in circumstances such as pregnancy, cirrhosis, and heart failure, extracellular fluid volume, plasma volume, and blood volume are all expanded, and yet the kidneys also retain sodium and water.

Cardiac output has also been examined as the primary regulatory determinant of body fluid volume and renal sodium and water excretion. Cardiac output is decreased with volume depletion associated with diarrhea or hemorrhage, but it is increased in high-output cardiac failure, cirrhosis, and pregnancy; yet, the kidneys retain sodium and water in these three circumstances.

The glomerular filtration rate (GFR) has been proposed as the primary determinant of sodium and water regulation in the body. Thus, with volume depletion, the GFR decreases, and water and sodium retention occurs. The GFR, however, can be increased by 30% to 50% in pregnancy, and yet sodium and water retention occurs and leads to a 30% to 50% expansion of blood volume and extracellular fluid volume.[2] The sensitive regulation of vasopressin (antidiuretic hormone) was shown whereby a 1% to 2% change in extracellular fluid osmolality alters vasopressin release[3]; yet, one of the hallmarks of the edematous disorders is overt hypo-osmolality.[4] Thus, factors other than vasopressin and extracellular

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ABBREVIATIONS USED IN TEXT

ANP = atrial natriuretic peptide
cyclic GMP = cyclic guanosine monophosphate
GFR = glomerular filtration rate

fluid osmolality must be involved in regulating renal water excretion, or perhaps there is a "resetting" of the vasopressin osmostat.

The discovery of aldosterone seemed to be a key to renal sodium excretion and thus to extracellular fluid volume regulation.[5] Yet, when excessive amounts of aldosterone are administered to normal persons, only limited sodium retention occurs, and no edema appears—that is, "aldosterone or mineralocorticoid escape" occurs On the other hand, when exogenous aldosterone is administered to patients with cirrhosis or cardiac failure, they do not escape from the sodium-retaining effect of aldosterone, and thus ascites and pulmonary edema, respectively, worsen. The hormone, atrial natriuretic peptide (ANP), was then discovered,[6] and it was thought that sodium retention in heart failure and cirrhosis might be due to a deficiency of this hormone. When the ANP level was measured, however, the plasma concentrations were increased, not decreased, in both heart failure and cirrhosis.[7] Moreover, although exogenous ANP administration causes an increase in urinary flow and sodium excretion in normal subjects, when it is administered to patients with heart failure and cirrhosis, there is a renal resistance to the hormone.[8-10] These examples are just a few of the apparent paradoxes that must be addressed when attempting to understand how body fluid volume and composition are regulated. In this presentation, we propose a unifying hypothesis of volume regulation that addresses these paradoxes. The validity of this hypothesis will be examined in the circumstances of low- and high-output cardiac failure, cirrhosis, and pregnancy.

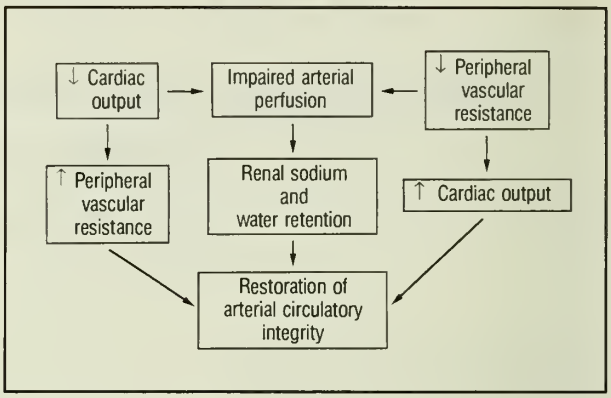

Figure 1.—A decrease in cardiac output or peripheral arterial resistance initiates sodium and water retention in disorders involving edema (from Schrier[18] with permission).

Low-Output Cardiac Failure

At the turn of the century, Starling in Great Britain proposed the backward theory of heart failure.[11] He proposed that in heart failure an increase in venous pressure with fluid transudation from the capillaries into the interstitium leads to a contraction of blood volume, thus triggering renal sodium and water retention. Administering albumin was therefore proposed as a means to treat heart failure. In contrast, it was later proposed that cardiac failure causes primary sodium and water retention that actually leads to an expansion of blood and plasma volumes.[12] This volume expansion then increases venous pressure with subsequent transudation of fluid from capillaries into the interstitium and edema formation. It was therefore proposed that vene-

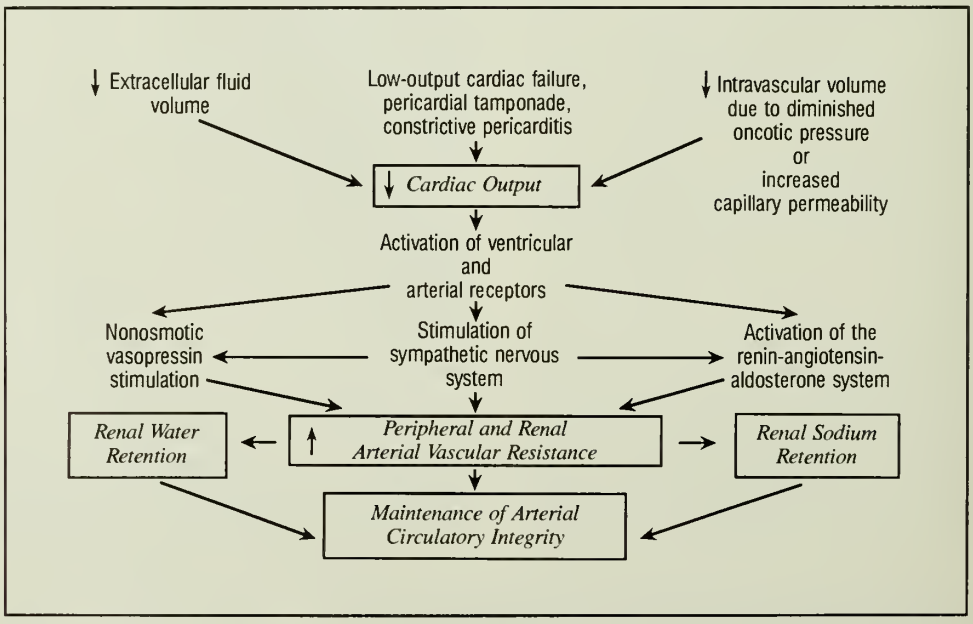

Figure 2.—The sequence of events is shown in which a decrease in cardiac output initiates renal sodium and water retention (from Schrier[15] with permission).

Variable	New York Heart Association Classification II	III	IV
Cardiac index	↓	↓↓	↓↓↓
Plasma hormones (AVP, renin, aldosterone, NE)	Normal	↑	↑↑
Plasma volume	↑	↑↑	↑↑↑

Figure 3.—Neurohumoral and plasma volume responses to progressive cardiac failure are classified according to the New York Heart Association (from Schrier[16] with permission). AVP = arginine vasopressin, NE = norepinephrine

section be considered the treatment of choice for cardiac failure.

Now that most of the body fluid volume compartments can be measured, blood and plasma volumes are known to expand in heart failure. About 85% of the plasma volume is located on the venous side of the circulation and 15% on the arterial side. There is, however, no readily sensitive technique to measure arterial blood volume, which constitutes only 2% of total body fluid. Nevertheless, with this background it is possible to hypothesize that the total plasma volume could be expanded in heart failure if it were mostly on the venous side of the circulation, but underfilling of the arterial circulation could occur due to a decrease in cardiac output. On the other hand, as discussed, cardiac output can be increased in certain circumstances in which sodium and water retention occurs, namely pregnancy, cirrhosis, and high-output heart failure.

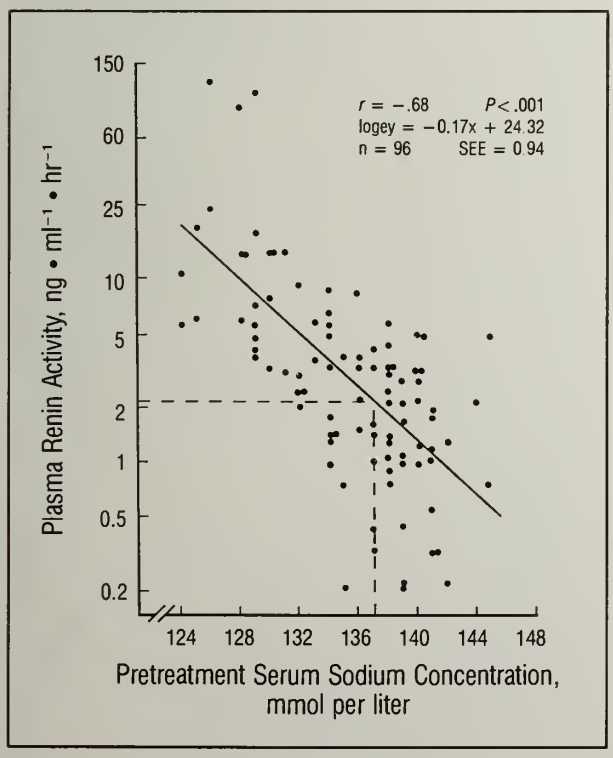

Figure 4.—The relationship is shown between serum sodium concentration and plasma renin activity before vasodilator therapy in 96 patients with severe chronic heart failure (from Lee and Packer[19] with permission). SEE = standard error of the estimate

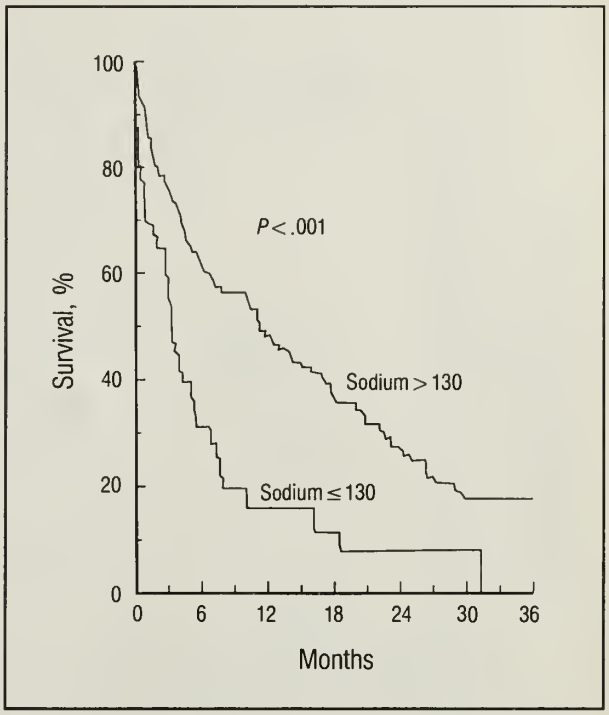

Figure 5.—Kaplan-Meier analysis shows cumulative rates of survival in patients with heart failure stratified into 2 groups based on pretreatment serum sodium concentration—>130 mmol per liter (n=163) versus ≤130 mmol per liter (n=40). Patients with severe hyponatremia had a highly unfavorable long-term prognosis (P<.001, Wilcoxon-Breslow) (from Lee and Packer[19] with permission).

If the arterial circulation is the dominant compartment in body fluid volume regulation, there must be a second determinant of arterial underfilling in addition to a diminished cardiac output. This second determinant is proposed to be an increased holding capacity of the arterial circulation as determined by capacitance and arterial vascular resistance. Thus, we propose a unifying hypothesis of body fluid volume regulation that indicates that either a decrease in cardiac output or peripheral arterial vasodilation causes arterial underfilling, and all the subsequent events occur in an attempt to restore arterial circulatory integrity (Figure 1).[13-18] In low cardiac output failure, there would be a secondary increase in peripheral vascular resistance, whereas with arterial vasodilation there is a secondary increase in cardiac output. In both circumstances, renal sodium and water retention occurs in an attempt to restore arterial circulatory integrity.

Virtually all circumstances of sodium and water retention in which the kidneys are normal can be incorpo-

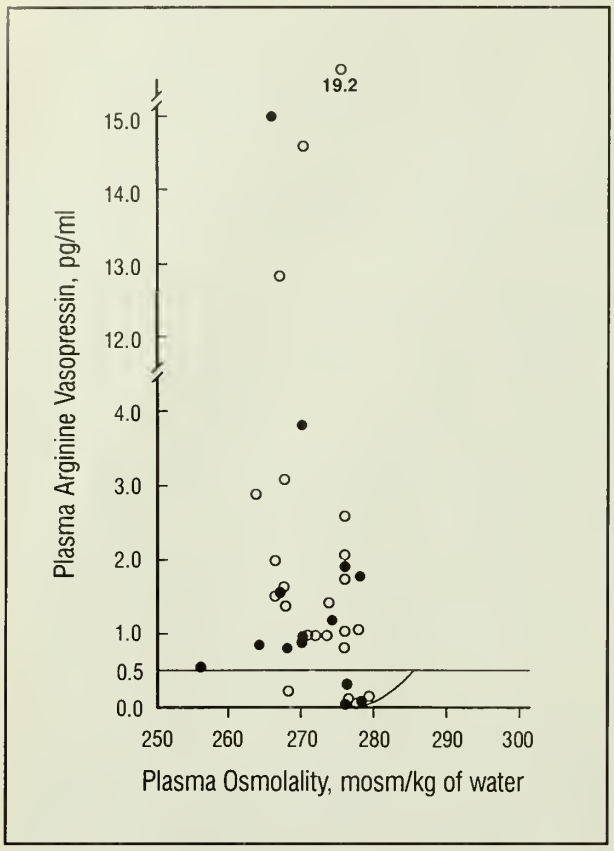

Figure 6.—Plasma arginine vasopressin (AVP) levels are shown in 37 hyponatremic patients with congestive heart failure. ● = patients who never received diuretics before the measurement of AVP levels (n=14); ○ = those patients who received diuretics within 24 hours of blood sampling for AVP measurement (n=23) (from Szatalowicz et al[23] with permission).

rated into this unifying hypothesis. A decrease in cardiac output leading to arterial underfilling may occur with diarrhea, low-output heart failure, pericardial tamponade, constrictive pericarditis, a loss of oncotic pressure due to a protein-losing dermopathy or enteropathy, or with a hypersensitivity reaction causing the loss of colloid from capillaries to the interstitium (Figure 2).[15] The resultant arterial underfilling is sensed by receptors in the ventricle, baroreceptors in the carotid artery and the aortic arch, and renal afferent arterioles. The resultant increased renal sympathetic tone is known to stimulate the renin-angiotensin-aldosterone system and the nonosmotic release of vasopressin. Although less sensitive, the nonosmotic stimulation of vasopressin with arterial underfilling overrides the osmotic regulation of vasopressin release.

As will be discussed, angiotensin and increased adrenergic tone contribute to the impaired escape from the sodium-retaining action of aldosterone, and the nonosmotic release of vasopressin contributes to the water retention. All these responses to arterial underfilling are directed toward the restoration of arterial circulatory integrity.

As cardiac output progressively decreases in a patient with heart failure, a progressive increase in the compensatory neurohumoral profile as assessed by measuring plasma vasopressin, renin, aldosterone, and norepinephrine levels would be expected (Figure 3).[16] Thus, those patients with heart failure with the highest plasma renin activity have the lowest pretreatment plasma sodium concentrations secondary to the stimulation of thirst and the nonosmotic release of vasopressin.[19] Moreover, high plasma renin activity and aldosterone and norepinephrine levels before treatment with diuretics indicate a poor prognosis.[20,21] Patients with this condition have arterial underfilling due to low cardiac indices; the resultant sodium and water retention causes the plasma volume to expand, mostly on the venous side of the circulation.

As shown in Figure 4, pretreatment plasma sodium concentrations in patients with heart failure correlate with plasma renin activities.[19] Moreover, the worst prognosis in a patient with heart failure before treatment occurs with low plasma sodium concentrations.[19] As shown in Figure 5, a pretreatment serum sodium concentration below 130 mmol per liter (130 mEq per liter) in patients with heart failure predicts a worse prognosis than for

TABLE 1.—*Water Excretion and Hemodynamic and Biochemical Characteristics of 2 Groups* of Patients with Heart Failure Classified Along Values of Plasma Vasopressin†*

Clinical Characteristic	*Group I (n=17)*	*Group II (n=8)*	P
Water excretion, %	31.4 ± 3.2	57.1 ± 7.3	<.005
Minimal urinary osmolality, mosm/kg of water	371 ± 36	162 ± 29	<.001
Maximum free water clearance, ml/min	−0.04 ± 0.28	2.03 ± 0.65	<.01
Osmolar clearance, ml/min	1.75 ± 0.2	1.61 ± 0.22	NS
Creatine clearance, ml • min^{-1} • 1.73 m^{-2}	55.4 ± 4.9	53.7 ± 10.4	NS
Cardiac index, liters • min^{-1} • m^{-2}	1.9 ± 0.1	2.47 ± 0.2	<.05
Pulmonary wedge pressure, mm of mercury	30.2 ± 1.4	21.7 ± 1.5	<.02
Right atrial pressure, mm of mercury	13.2 ± 1.2	10.2 ± 1.3	NS
Mean arterial blood pressure, mm of mercury	85.8 ± 2.7	90.8 ± 4.0	NS
Pulse, beats/min	81 ± 3	82 ± 5	NS
Plasma renin activity, ng • ml^{-1} • hr^{-1}	4.4 ± 0.7	1.99 ± 0.4	<.01
Plasma aldosterone, ng/dl	74.1 ± 11.6	10.2 ± 2.1	<.001
Arterial Po_2, mm of mercury	80.3 ± 2.7	80.8 ± 5.9	NS

NS = not significant

*Group I patients had high plasma vasopressin levels (mean, 3 pg/ml); group II patients had undetectable plasma vasopressin levels (<0.5 pg/ml).
† From Bichet et al with permission.[28]

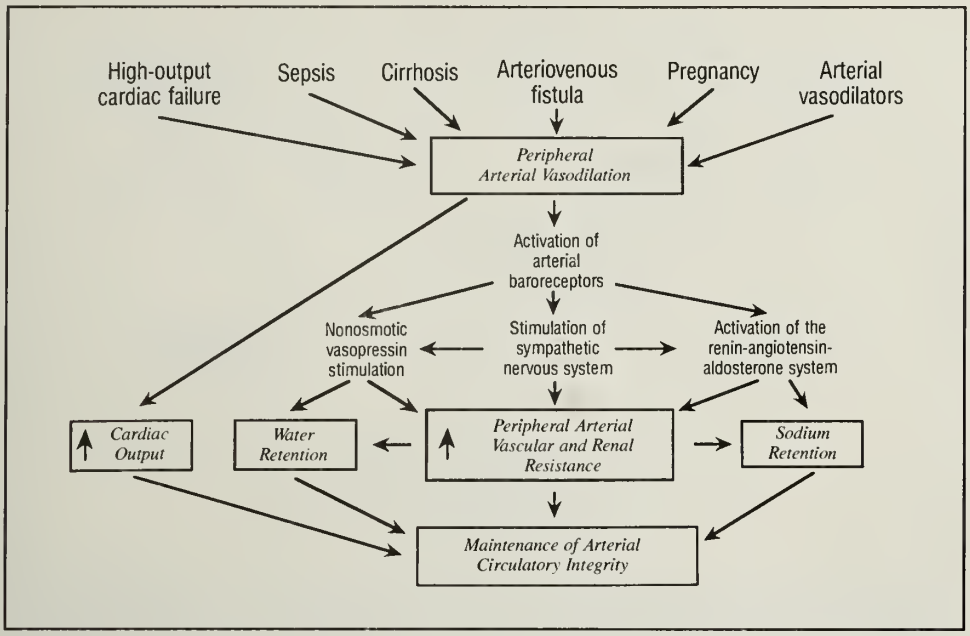

Figure 7.—The sequence of events is shown in which peripheral arterial vasodilation initiates renal sodium and water retention (from Schrier[15] with permission).

those patients with serum sodium concentrations above 130 mmol per liter.

Evidence exists that the increased plasma norepinephrine concentrations in heart failure are a reasonable index of sympathetic activity. Measurements of tritiated secretion rates of norepinephrine in patients with heart failure demonstrated substantially higher secretion rates than in normal persons, whereas the norepinephrine clearance rates were comparable.[22] Thus, increased plasma norepinephrine concentrations in patients with heart failure are primarily due to increased sympathetic activity. As for the role of the sympathetic nervous system in the nonosmotic release of vasopressin, pathways from arterial baroreceptors in the carotid artery and aortic arch travel through the glossopharyngeal and vagus nerves to the nucleus tractus solitarius in the midbrain and then to the hypothalamus, where vasopressin is synthesized in the paraventricular and supraoptic nuclei. With immunohistochemical staining, vasopressin neurons in the paraventricular and supraoptic nuclei can be shown to be interspersed with catecholamine nerve endings. The axons of the vasopressin-synthesizing cell bodies terminate in the posterior pituitary where the hormone is stored and released. This reflex terminates in the nonosmotic release of vasopressin, which is less sensitive but more potent than the osmotic regulation of vasopressin.

Using the vasopressin bioassay, vasopressin was not incriminated in the hyponatremia of heart failure. The bioassay, however, could only detect plasma vasopressin concentrations above 10 pg per ml. When a sensitive radioimmunoassay for vasopressin was developed, it was clear that normal urine concentration and dilution occur in response to plasma vasopressin levels between 0.5 and 4 pg per ml, values that were not detectable with the bioassay. As shown in Figure 6, 30 of 37 patients with heart failure did not have suppressed plasma concentrations of vasopressin, even though they had hypo-osmolarity and hyponatremia; thus, a nonosmotic release of vasopressin occurred in these patients.[23]

TABLE 2.—*Hemodynamics in Rats With High Output Heart Failure**

Hemodynamics	*Control Rats*	*Aorta-caval Fistulae*	P
Mean arterial pressure, mm of mercury	116 ± 9	102 ± 8	<.001
Cardiac output, ml • min^{-1} • 100 grams^{-1} of body weight	39.6 ± 6.7	50.0 ± 9.0	<.001
Peripheral vascular resistance, mm of mercury • min^{-1} • 100 grams^{-1} of body weight	3.11 ± 0.71	1.98 ± 0.37	<.002
Heart weight, grams	1.15 ± 0.13	1.89 ± 0.28	<.001

* Riegger et al with permission.[29]

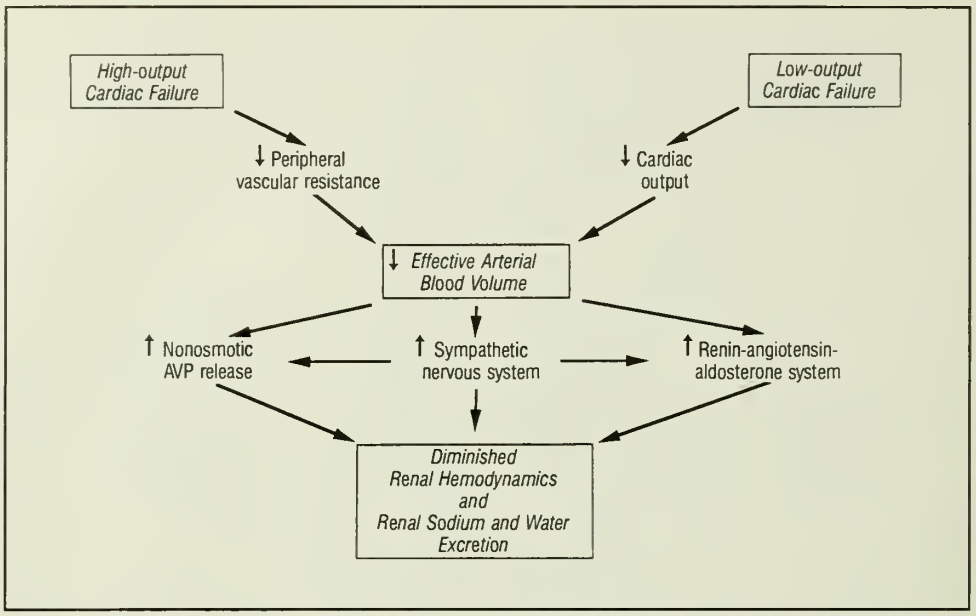

Figure 8.—The mechanisms of high- and low-output cardiac failure are shown. Although the initiating "underfill" event differs in high- and low-output failure, the subsequent pathways leading to renal sodium and water retention are similar (from Schrier[13] with permission). AVP = arginine vasopressin

When complementary DNA probes are used for the preprohormone of vasopressin in the hypothalamus, experimental cardiac failure in animals exhibits increased messenger RNA for vasopressin compared with that in control animals.[24] Thus, both increased nonosmotic vasopressin gene expression and vasopressin release are associated with heart failure.

The V_2 receptor is the antidiuretic receptor for vasopressin, whereas the V_1 receptor is the vascular receptor. In experimental low-output heart failure, impaired diluting ability as demonstrated with an acute water load can be corrected with a V_2 vasopressin antagonist.[25] Thus, in this experimental model of acute heart failure, the nonosmotic release of vasopressin appears to account completely for the impaired water excretion. Orally active nonpeptidic vasopressin antagonists have now been developed in Japan.[26,27]

Patients with hyponatremia in heart failure and with detectable plasma vasopressin concentrations (mean, 3 pg per ml) should have more evidence of arterial underfilling—stimulation of the neurohumoral profile—than patients with heart failure with undetectable

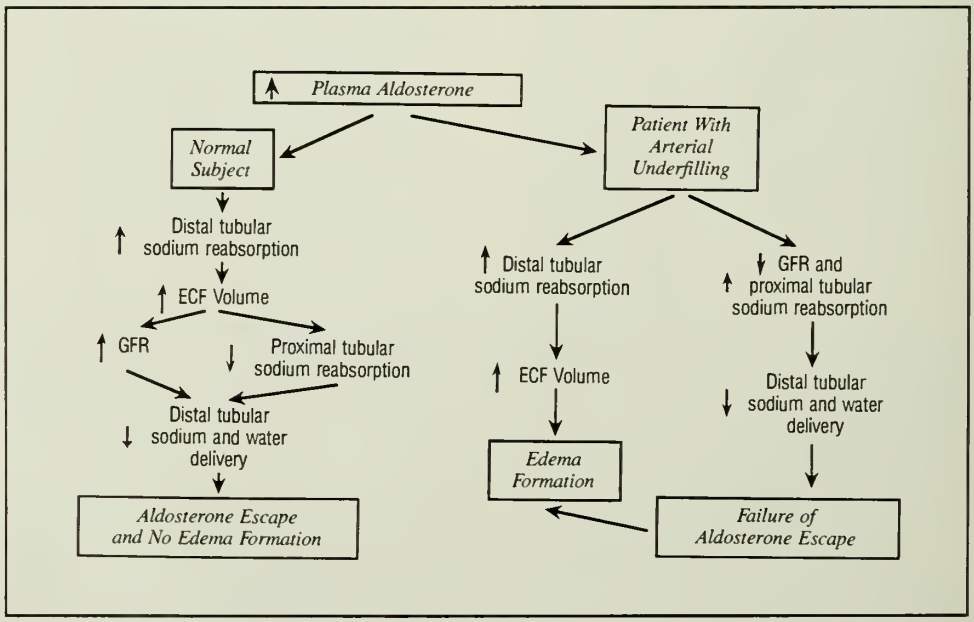

Figure 9.—Events involved in normal (left) and impaired (right) aldosterone escape are shown (from Schrier[15] with permission). ECF = extracellular fluid, GFR = glomerular filtration rate

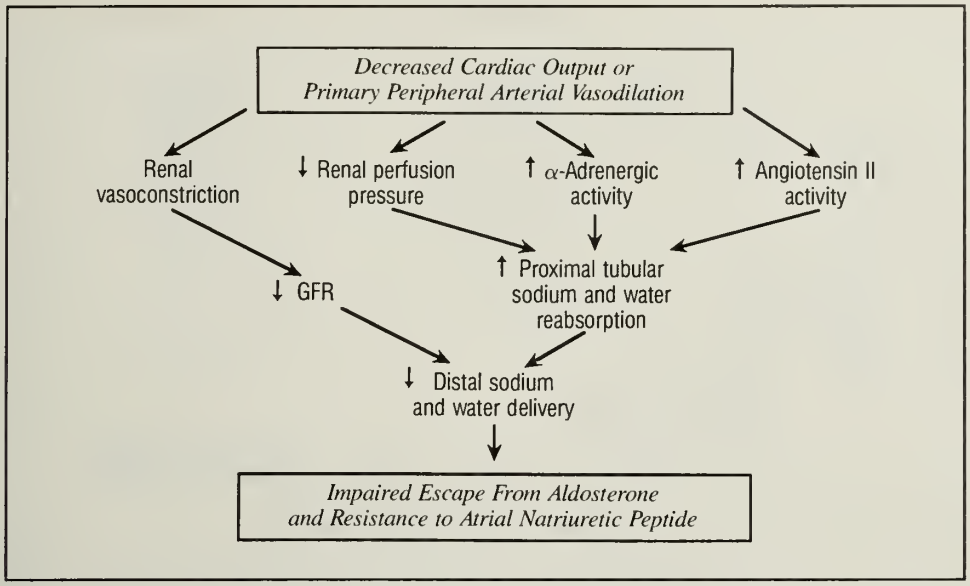

Figure 10.—A decrease in cardiac output or peripheral arterial vasodilation can initiate events that diminish distal sodium delivery, thereby impairing aldosterone escape and causing resistance to atrial natriuretic peptide (from Schrier and Bettor[30] with permission). GFR = glomerular filtration rate

vasopressin levels (<0.5 pg per ml). As shown in Table 1, those patients with evidence of nonosmotic vasopressin release showed significantly lower cardiac indexes, higher pulmonary wedge pressures, and higher plasma renin and aldosterone concentrations.[28] Moreover, when these patients with detectable plasma concentrations of vasopressin were treated with agents to decrease the cardiac afterload, the resultant increase in the cardiac index was associated with improved water excretion and the suppression of plasma and platelet vasopressin.[28]

High-Output Cardiac Failure

In the context of this unifying hypothesis of body fluid volume regulation, the second initiator of arterial underfilling is peripheral arterial vasodilation. Thus, systemic arterial vasodilation should account for the remainder of the circumstances in which sodium and water retention occurs despite normal kidney function. As shown in Figure 7, these clinical states include high-output cardiac failure, sepsis, cirrhosis, large arteriovenous fistulae, pregnancy, and large doses of arterial vasodilators such as minoxidil and hydralazine. The neurohumoral compensatory responses of arterial underfilling due to arterial vasodilation are the same as occurs with arterial underfilling due to a decrease in cardiac output.

In Table 2 are results obtained in an experimental model of high-output cardiac failure.[29] The diminished systemic vascular resistance is associated with an increased cardiac output, cardiac hypertrophy, and activation of the neurohumoral profile of arterial underfilling, namely increased plasma renin activity, aldosterone, norepinephrine, and vasopressin. Thus, one of the paradoxes of body fluid volume regulation can now be ad-

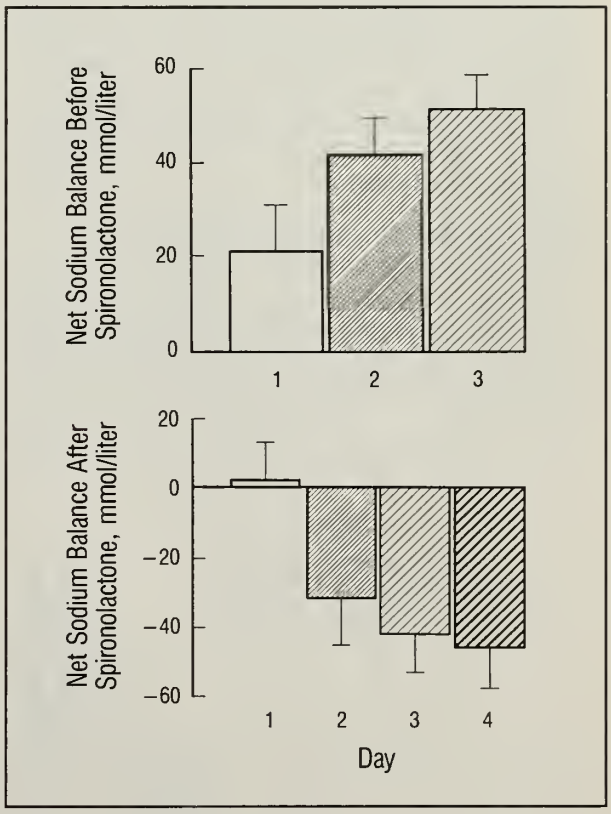

Figure 11.—A reversal of sodium retention by aldosterone antagonism occurs in patients with congestive heart failure. Net positive cumulative sodium balance is seen for the periods before spironolactone is given (**top panel**), and net negative cumulative sodium balance is seen after the initiation of spironolactone therapy (400 mg per day; **bottom panel**). The increase in sodium excretion with spironolactone therapy was significant ($P<.01$) (from Hensen et al[34] with permission).

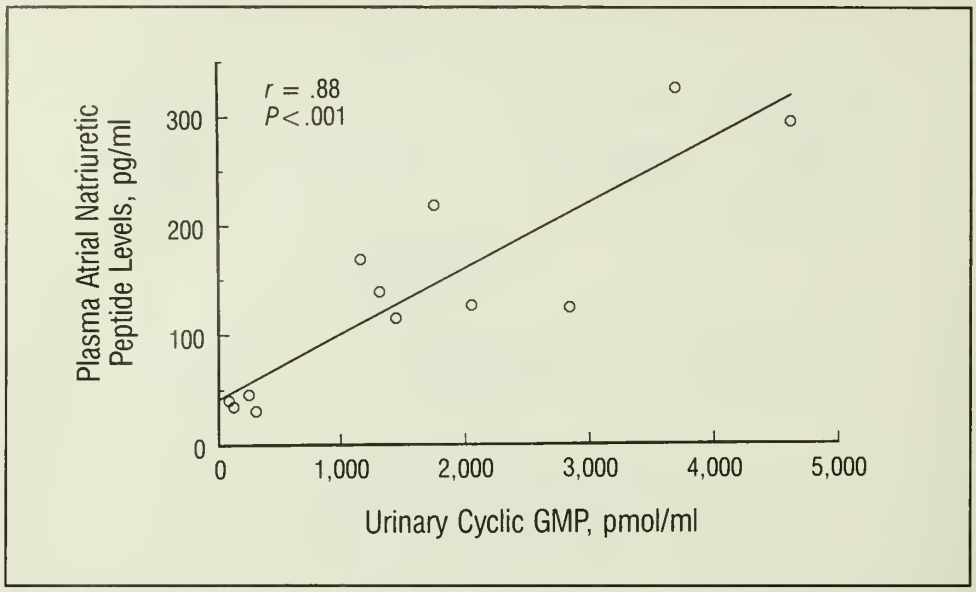

Figure 12.—Plasma atrial natriuretic peptide levels correlate with urinary cyclic guanosine monophosphate (cyclic GMP) levels in patients with heart failure (from Abraham et al[37] with permission).

dressed whereby sodium and water retention can occur in patients in whom cardiac output is low, as with low-output cardiac failure, or high, as with thyrotoxicosis and beriberi. Thus, although the causes of arterial underfilling are different in low- and high-output cardiac failure, the secondary responses to arterial underfilling are comparable (Figure 8).[13]

Aldosterone Escape and Atrial Natriuretic Peptide Resistance in Cardiac Failure

The renal site of action of vasopressin, aldosterone, and ANP is the collecting duct in the terminal portion of the nephron. Either a decrease in the GFR or an increase in proximal tubular reabsorption, or both, can diminish distal sodium and water delivery to the site of action of these hormones in the collecting duct. Because escape from the sodium-retaining effect of aldosterone is dependent on an increased rate of delivery of sodium to the distal nephron, the responses to arterial underfilling may diminish sodium delivery to the collecting duct, thereby explaining the impaired aldosterone escape that is characteristic of arterial underfilling (Figure 9).[15]

In circumstances of arterial underfilling due to either a decrease in cardiac output or primary peripheral arterial vasodilation, a number of factors would lead to a decreased sodium and water delivery to the collecting duct (Figure 10).[30] Advanced heart failure is associated with renal vasoconstriction and a decrease in renal perfusion

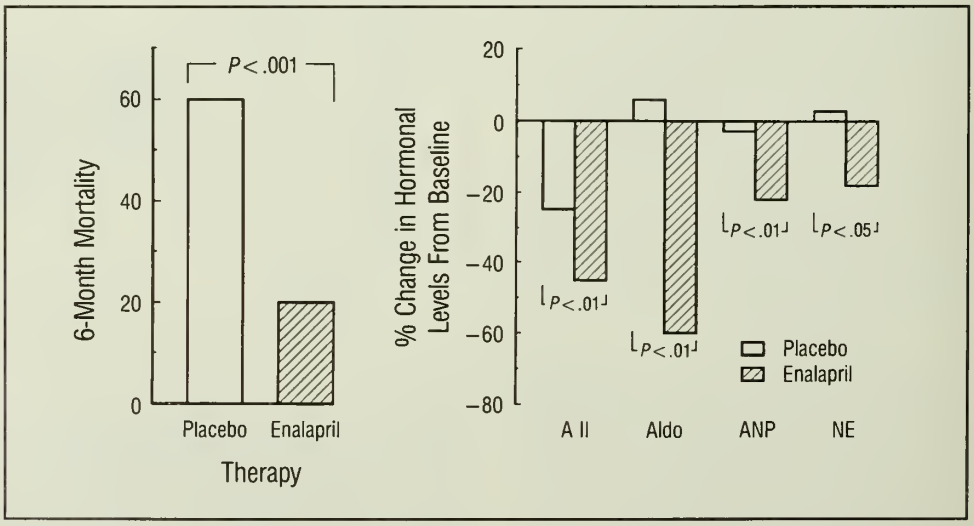

Figure 13.—Enalapril therapy reduces 6-month mortality and hormonal levels in patients with severe congestive heart failure (from Swedberg et al[40] with permission). A II = angiotensin II, Aldo = aldosterone, ANP = atrial natriuretic peptide, NE = norepinephrine

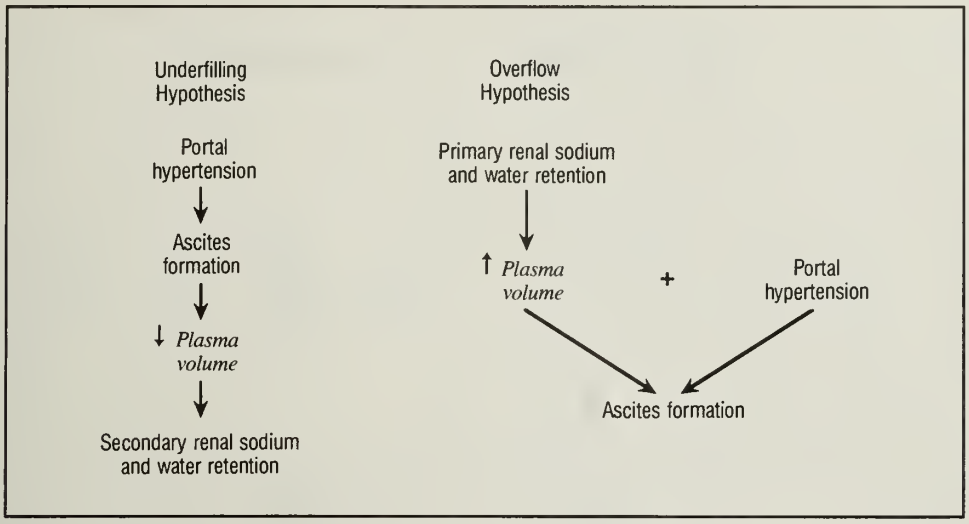

Figure 14.—The characteristics of underfilling (left) and overflow (right) hypotheses of renal sodium and water retention in cirrhosis are shown (from Schrier[17] with permission).

that decrease distal tubular sodium and water delivery. Moreover, direct effects of adrenergic stimulation[31] and angiotensin[32,33] increase proximal tubular sodium and water reabsorption. Thus, impaired aldosterone escape secondary to the consequences of arterial underfilling suggest that aldosterone-mediated sodium retention is important in heart failure. Support for this conclusion derives from the demonstration that large doses of spironolactone (400 mg per day) reverse sodium retention in patients with heart failure (Figure 11).[34]

A resistance to the normal diuretic and natriuretic response to exogenous ANP is another hallmark of heart failure both in experimental models[35,36] and in humans.[8,9] There are several explanations for this ANP resistance: inhibition of renal ANP receptors; immunoreactive plasma ANP that is biologically inactive; or increased neutral endopeptidase activity in the proximal tubule that degrades ANP, thus limiting the hormone delivery to the distal collecting-duct sites of action. These three possibilities for ANP resistance should be associated with decreased activation of the secondary messenger for ANP, namely cyclic guanosine monophosphate (cyclic GMP). When cyclic GMP levels are measured in the urine of patients with heart failure, levels are increased and are correlated with plasma ANP concentrations. When this correlation between plasma ANP and urinary cyclic GMP was studied in patients with heart failure, a linear relationship was found (Figure 12).[37] This last finding supports the concept that diminished renal distal tubular sodium and water delivery is the mechanism of ANP resistance in heart failure, rather than the aforementioned other possibilities.

Because increased renal adrenergic tone is known to increase proximal tubular sodium reabsorption, renal denervation in animals with experimental heart failure might be expected to reverse the ANP resistance. Recent studies have indeed shown that renal denervation reverses the resistance to ANP in experimental heart failure.[38] The first detectable hormonal increase in heart failure is the plasma ANP level, thus raising the possibility that the early onset of sodium retention in cardiac decompensation is delayed by ANP. The following study provides some experimental evidence to support this possibility in early heart failure, even though ANP resistance characterizes advanced heart failure.[39] A comparable decrease in mean arterial pressure was produced in dogs by ventricular tachycardia and thoracic vena caval constriction. Whereas plasma ANP levels rose only with ventricular tachycardia, a decrease in sodium excretion occurred only with caval constriction. The role of the increased ANP concentration with ventricular tachycardia to delay sodium retention was supported by the finding that caval constriction no longer caused sodium retention if exogenous ANP was simultaneously infused to produce a plasma ANP concentration comparable to that observed with ventricular tachycardia.

Variable	Compensated Cirrhosis (no ascites)	Decompensated Cirrhosis (ascites)	Hepatorenal Syndrome
Peripheral arterial vasodilation	↑	↑↑	↑↑↑
Plasma hormones—AVP, renin, aldosterone, NE	Normal	↑	↑↑
Plasma volume	↑	↑↑	↑↑↑

Figure 15.—The "peripheral arterial vasodilation hypothesis" is shown. Normal plasma hormone concentrations indicate relative stimulation in the presence of plasma volume expansion. Hypoalbuminemia may attenuate plasma volume expansion (from Schrier[44] with permission). AVP = arginine vasopressin, NE = norepinephrine

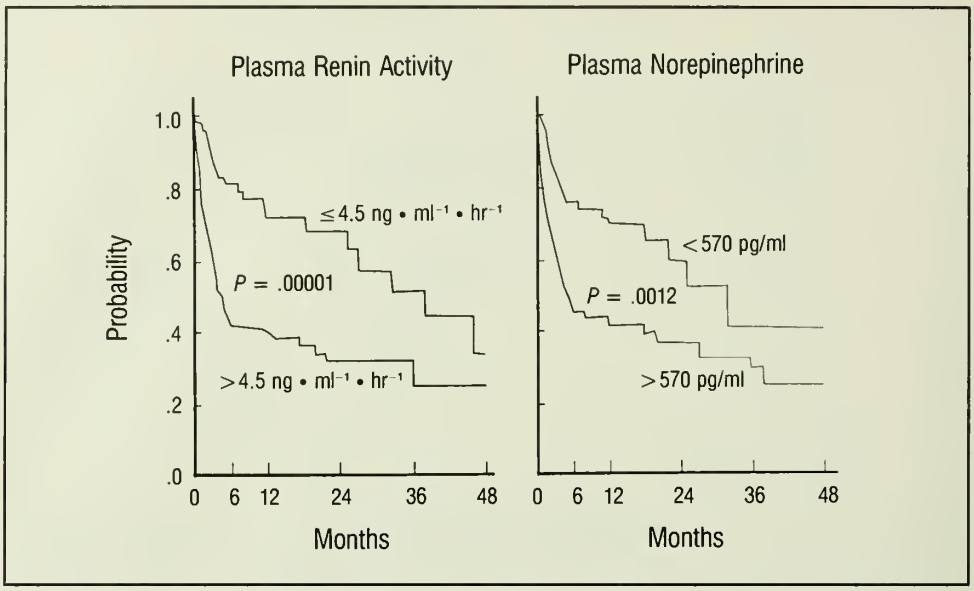

Figure 16.—The plasma renin and norepinephrine concentrations are prognostic indicators in patients with cirrhosis (from Llach[45] with permission).

To summarize, with heart failure, arterial underfilling may occur due to a decrease in cardiac output with myocardial disease or peripheral arterial vasodilation with thyrotoxicosis and beriberi. In the latter circumstance, however, cardiac dysfunction may also accompany the arterial vasodilation. With advanced myocardial disease, the compensatory neurohumoral responses in cardiac failure may become maladaptive. For example, the sodium and water retention may cause pulmonary congestion, whereas the rise in peripheral vascular resistance increases cardiac afterload and myocardial metabolic demand. Results of the CONSENSUS study demonstrate that treatment with angiotensin-converting enzyme inhibitor decreases six-month mortality in association with a decrease in plasma levels of angiotensin, aldosterone, norepinephrine, and ANP (Figure 13).[40]

Cirrhosis

In Figure 14 are shown the two primary hypotheses that have been proposed to explain the sodium and water retention and ascites formation with cirrhosis.[17] With the classic "underfilling hypothesis," portal hypertension causes ascites with an associated decrease in plasma volume that causes secondary renal sodium and water retention.[41] When the plasma volume was found

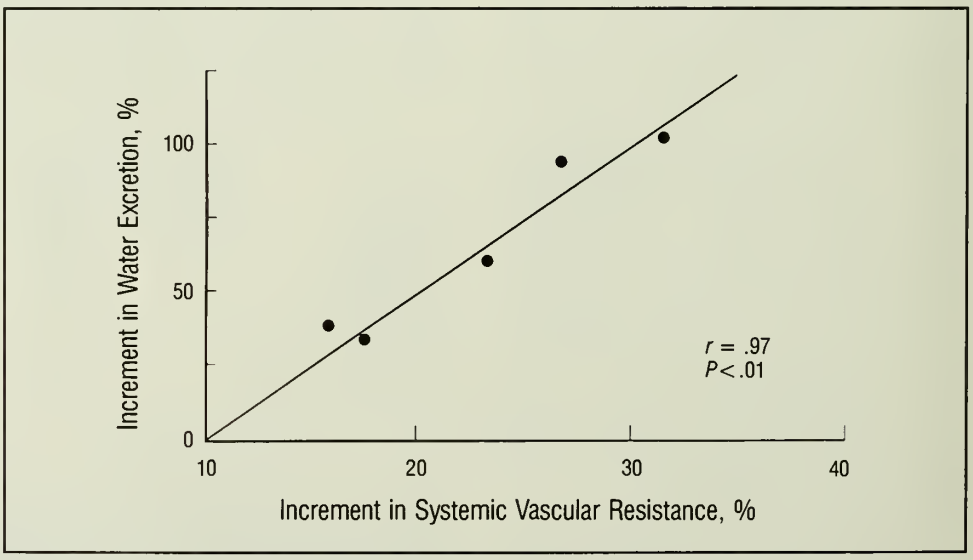

Figure 17.—A correlation is seen between the increase in systemic vascular resistance and the increase in water load excretion from immersion alone to immersion with norepinephrine infusion (from Shapiro et al[52] with permission).

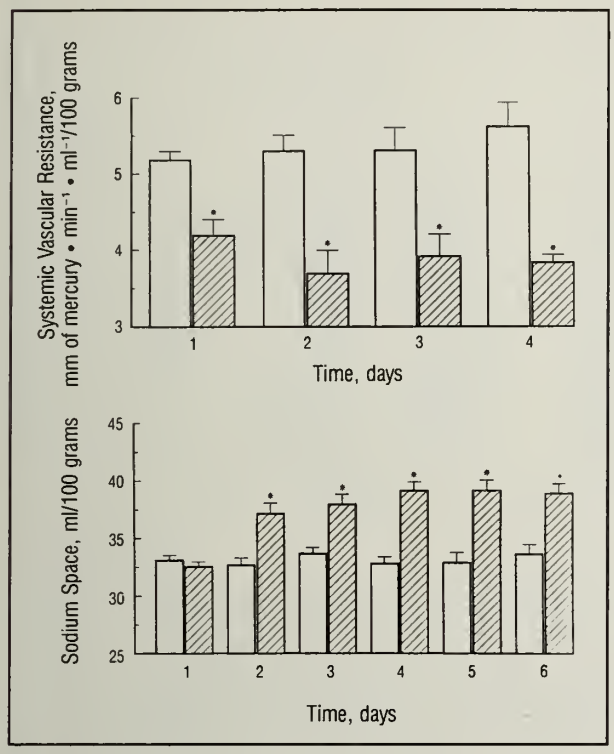

Figure 18.—A temporal relationship is shown between decreased peripheral vascular resistance (**top panel**) and increased sodium space (**bottom panel**) in rats with prehepatic portal hypertension (**shaded bars**) versus sham-operated rats (**white bars**) (from Albillos et al[54] with permission). * = $P<.05$

to be expanded in cirrhosis and this volume expansion antedated the ascites formation, this underfilling hypothesis was no longer tenable. Thus, the "overflow hypothesis" was proposed.[42] This hypothesis proposes that a diseased liver, or some consequence such as an increase in intrahepatic pressure, causes primary sodium and water retention with the expansion of the plasma volume. Ascites then occurs because of the overflow of the plasma volume expansion into the abdominal cavity due to portal hypertension. This overflow hypothesis, however, cannot account for the clinical spectrum of cirrhosis from compensated to decompensated to the hepatorenal syndrome states. This is because the expansion of the plasma volume, on both the venous and arterial sides of the circulation, cannot explain the progressive activation of the neurohumoral profile that characterizes both progressive cirrhosis and arterial underfilling.

The "peripheral arterial vasodilation hypothesis" was therefore proposed.[43] As shown in Figure 15, this hypothesis explains the rise in cardiac output, the fall in mean arterial pressure, and stimulation of the neurohumoral profile of arterial underfilling over the entire clinical spectrum of liver disease.[44] With this hypothesis, patients with cirrhosis with pretreatment hyponatremia and the highest plasma renin, aldosterone, norepinephrine, and vasopressin levels should have the worst prognosis. That is indeed the case. As shown in Figure 16, those patients with cirrhosis with the highest plasma renin and norepinephrine activities have the poorest survival rates.[43]

Using a complementary DNA probe for the preprohormone, levels of the hypothalamic messenger RNA for vasopressin were shown to be increased in experimental cirrhosis.[44] Thus, in cirrhosis, there is not only an increased release of vasopressin from the pituitary, but also an enhanced hypothalamic biosynthesis occurs, as is also characteristic of heart failure.

It is clear that patients with cirrhosis differ in their degree of arterial underfilling and may be separated by their capacity to excrete a water load of 20 ml per kg of body weight. Those patients with cirrhosis who have impaired water excretion demonstrate more evidence of arterial underfilling than patients with cirrhosis who normally excrete the same 20-ml-per-kg water load.[47] Nonexcreting patients have lower plasma sodium concentrations, higher urinary osmolalities, and higher plasma renin, aldosterone, norepinephrine, and vasopressin concentrations than patients who excrete a water load normally.[47] In 26 patients with cirrhosis, there was a significant correlation between plasma norepinephrine, as an index of sympathetic activity, and plasma vasopressin and renin activity. The administration of a V_2 vasopressin antagonist has been shown to improve water excreting and diluting ability in experimental cirrhosis,[48] thus incriminating the nonosmotic release of vasopressin in water retention. There is also a role of the V_1 vasopressin receptor in maintaining blood pressures in patients with cirrhosis.[49] In experimental cirrhosis, the V_1 vasopressin vascular antagonist causes a fall in blood pressure, indicating that vasopressin, as well as angiotensin and the sympathetic nervous system, is an important factor in maintaining arterial circulatory integrity in cirrhosis.

In these same 26 patients with cirrhosis studied on a constant sodium intake, there was a significant positive correlation between plasma renin activity and plasma norepinephrine levels and a negative correlation between urinary sodium excretion and plasma norepinephrine levels.[47] These results are consonant with a role of angiotensin and adrenergic stimulation in decreasing sodium delivery to the distal nephron in cirrhosis, as occurs in heart failure. The sodium and water retention in cirrhosis clearly is also due to extrarenal events, as the kidneys of patients with the hepatorenal syndrome have been shown to be no longer retaining sodium when transplanted to recipients with normal livers,[50] or when normal livers are transplanted into these patients with the hepatorenal syndrome.[51]

On this background, a combined maneuver of head-out water immersion and administering exogenous norepinephrine to reverse arterial vasodilation was studied in hyponatremic, ascitic patients with cirrhosis in an effort to reverse the sodium and water retention.[52] The results demonstrated that this maneuver returned sodium and water excretion to normal in these patients with ad-

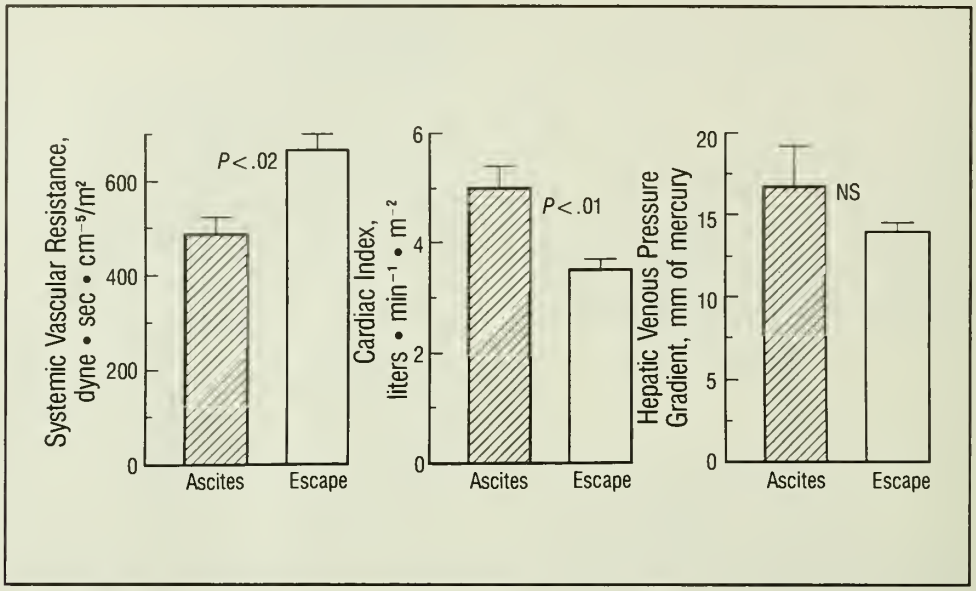

Figure 19.—Baseline systemic hemodynamic measurements and hepatic venous pressure gradient are shown, as an index of portal pressure, in a group of 19 cirrhotic patients without a history of sodium retention treated with mineralocorticoids (from La Villa et al[55] with permission). Escape (n = 15): patients who showed a mineralocorticoid escape phenomenon and did not develop ascites; Ascites (n = 4): patients in whom persistent sodium retention and ascites developed during mineralocorticoid administration; NS = not significant

vanced cirrhosis, thus supporting the concept that arterial underfilling due to arterial vasodilation in the splanchnic and other vascular beds is the cause of sodium and water retention. Further support from these results for the peripheral arterial vasodilation hypothesis was the finding of a strong correlation between the increment in water excretion and that in systemic vascular resistance (Figure 17). As in heart failure, there is evidence for an important role of aldosterone in the sodium retention that occurs in cirrhosis. Investigators showed that 16 of 21 patients with cirrhosis treated over three to four weeks with large doses of the competitive aldosterone antagonist spironolactone had resolution of their ascites, in contrast to only 4 of 22 matched, untreated patients with cirrhosis.[53]

Studies in rats with portal hypertension due to portal vein constriction provide information about the temporal relationship between portal hypertension, splanchnic vasodilation, and sodium retention.[54] As shown in Figure 18, a fall in systemic vascular resistance

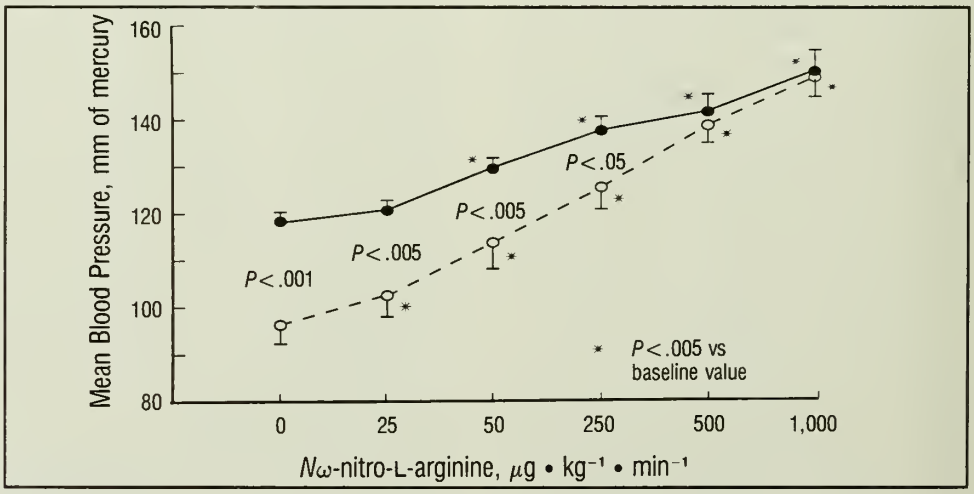

Figure 20.—Mean blood pressures are shown under basal conditions and after the administration of sustained, increasing doses of Nω-nitro-L-arginine in cirrhotic (-o-) and control (-•-) rats. Data are given as mean ± standard error of the mean. *P* values given in the figure are those obtained when comparing cirrhotic and control rats (from Clària et al[56] with permission). * = *P*<.005 versus baseline values

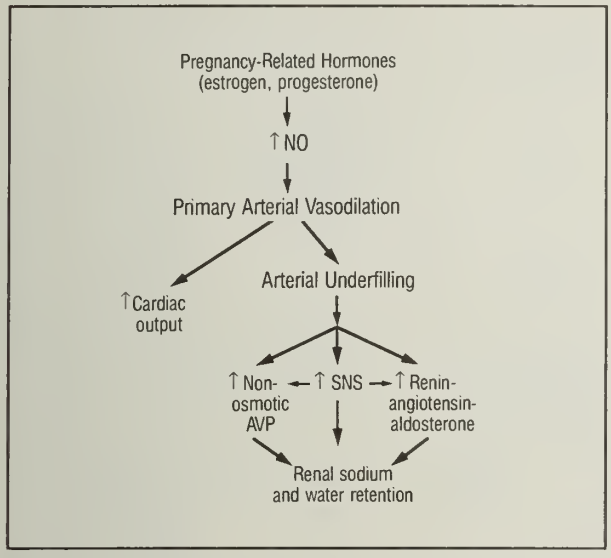

Figure 21.—The peripheral arterial vasodilation hypothesis in pregnancy is illustrated. AVP = arginine vasopressin, NO = nitric oxide, SNS = sympathetic nervous system

occurs within 24 hours after the onset of acute portal hypertension, whereas a rise in total body sodium first occurs within 48 hours after the onset of portal hypertension. These results are compatible with arterial underfilling due to arterial vasodilation initiating sodium retention in association with portal hypertension.

Studies in patients with compensated cirrhosis without ascites provide further important information about the mechanisms of sodium retention and ascites formation. These studies examined the capacity to escape from the sodium-retaining effect of mineralocorticoid hormone. In support of the peripheral arterial vasodilation hypothesis, ascites developed in those patients who did not have mineralocorticoid escape, and they had lower systemic vascular resistances and higher cardiac outputs than those patients who had mineralocorticoid escape (Figure 19).[55] No difference occurred in the hepatic venous pressure gradient, as an index of portal hypertension and intrahepatic pressure, between these two groups of cirrhotic patients. In vasodilated patients, plasma renin activity was also not suppressed, and their plasma ANP levels were not increased during mineralocorticoid administration.

What causes the systemic vasodilation in cirrhosis? There is now substantial evidence suggesting that at least one factor in the vasodilation associated with cirrhosis is the induction of nitric oxide synthase in either vascular smooth muscle, endothelial cells, or both. Administering L-arginine analogues, which block nitric oxide synthase, has been shown to increase the mean arterial pressure in a dose-response manner so that with maximal doses there is no difference in arterial pressures between control and cirrhotic animals (Figure 20).[56] Because plasma endotoxin concentrations have been shown to be increased in cirrhosis[57] and endotoxin may induce nitric oxide synthase in vascular smooth muscle,[58,59] these results support a role of nitric oxide—that is, endothelium-derived relaxing factor—in the vasodilation associated with cirrhosis. Other vasodilators, however, as well as portosystemic shunting, may also be involved in the later stages of cirrhosis.[60-69]

A resistance in ANP has also been shown to occur in cirrhosis in a manner similar to that in cardiac failure. There also does not seem to be any defect in the biologic activity of ANP receptor activation because exogenous ANP has been shown to increase urinary cyclic GMP levels even in those cirrhotic patients whose urinary flow or sodium excretion rates did not increase in response to increasing doses of exogenous ANP.[70,71] Evidence for diminished distal sodium and water delivery due to the consequences of arterial vasodilation (Figure 10) as a cause for the ANP resistance is the finding that this phenomenon can be reversed by renal denervation in experimental cirrhosis in rats.[72]

Local effects of arterial vasodilation also contribute to sodium and water retention in cirrhosis and other vasodilated states. Specifically, albumin distribution space and interstitial compliance have been shown to be increased in both cirrhotic rats[73] and normal rats treated with the arterial vasodilator minoxidil.[74] Thus, a relative increase in interstitial oncotic pressure and a decrease in interstitial hydrostatic pressure with the dilation of precapillary arteriolar sphincters would be expected to predispose to edema formation.

To summarize, peripheral arterial vasodilation in cirrhosis causes arterial underfilling and adaptive neurohumoral responses that can become maladaptive in extreme circumstances. Specifically, the resultant ascites formation predisposes to spontaneous bacterial peritonitis, the renal vasoconstriction predisposes to the hepatorenal syndrome, and the increased splanchnic vasodilation and flow are major contributors to the portal hypertension and esophageal varices, all of which combine to increase morbidity and mortality in patients with cirrhosis. A therapeutic strategy to reverse these extrahepatic consequences of cirrhosis could be designed to attenuate these causes of morbidity and mortality in this disorder. Administering an orally active, long-acting V_1 agonist, β-blockers, or somatostatin to decrease splanchnic flow and an early prophylactic LeVeen peritoneovenous shunt should decrease the arterial underfilling in cirrhosis.[75] This approach should then suppress the neurohumoral responses to arterial underfilling and thereby prevent the hepatorenal syndrome; allow for aldosterone escape, thus preventing ascites formation and spontaneous bacterial peritonitis; and decrease splanchnic flow with a lowering of the portal pressure, thus diminishing the morbidity and mortality of esophageal variceal bleeding.

Pregnancy

Pregnancy is associated with a 30% to 50% increase in extracellular fluid, plasma, and blood volume and a 30% to 50% increase in cardiac output, GFR, and renal blood flow. Primary renal sodium and water retention

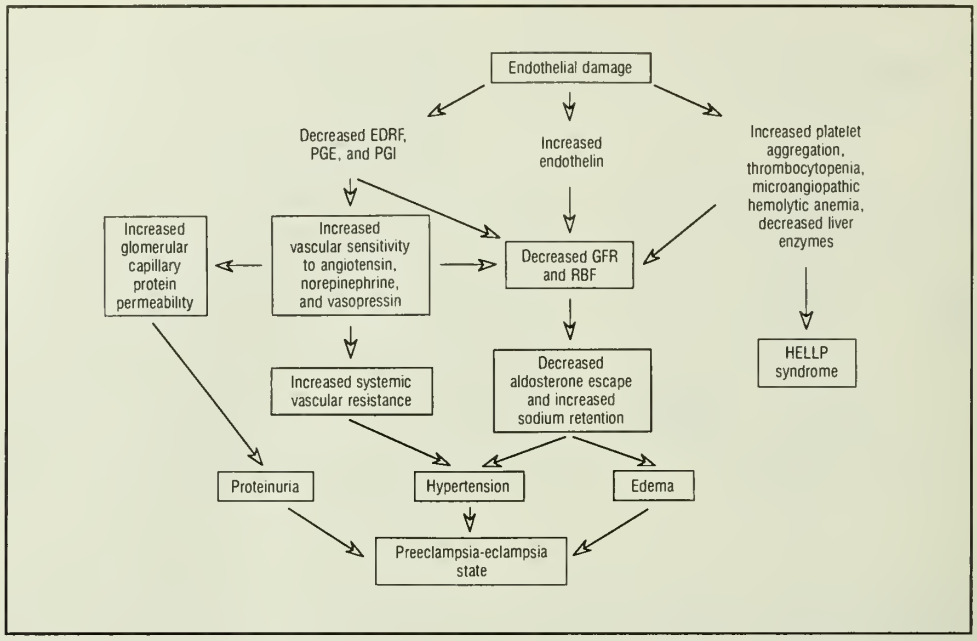

Figure 22.—The pathophysiologic schema for preeclampsia and eclampsia is shown (from Abraham et al[37] with permission). EDRF = endothelium-derived relaxing factor; GFR = glomerular filtration rate; HELLP = hemolysis, elevated liver enzymes, and low platelet count; PGE = prostaglandin E; PGI = prostaglandin I; RBF = renal blood flow

has been suggested to account for these changes associated with normal pregnancy. Several important factors, however, suggest that primary arterial vasodilation causing arterial underfilling with secondary sodium and water excretion occurs in pregnancy. For example, a fall in systolic and diastolic blood pressures occurs in the first trimester of pregnancy despite an increase in the blood volume.[76] The renin-angiotensin-aldosterone axis is activated early in pregnancy, an effect also expected with arterial underfilling due to peripheral arterial vasodilation,[77] whereas primary volume expansion would be expected to suppress these hormones. The increase in GFR and renal blood flow in pregnancy precedes the expansion of the blood volume,[78] thus suggesting primary renal vasodilation. Additional important findings in pregnancy are the "resetting" of the vasopressin-osmoreceptor[79] and the volume depletion-vasopressin relationships[80] in a direction suggestive of arterial underfilling due to systemic arterial vasodilation.

Emerging evidence suggests that nitric oxide mediates the peripheral arterial vasodilation of pregnancy. Long-term blockade of nitric oxide synthase with nitro-L-arginine methylester is associated with a return to normal of mean arterial pressures in pregnant rats compared with controls.[81] Moreover, in the same study, the administration of an L-arginine bolus was associated with a substantially greater fall in mean arterial pressures in pregnant than in nonpregnant rats. Hormones known to increase in pregnancy, such as estrogen and progesterone, have been shown to induce nitric oxide synthase in in vitro experiments.[82,83] Further support for a role for nitric oxide in the vasodilation of pregnancy derives from the correlation between urinary cyclic GMP, the secondary messenger of nitric oxide, and urinary nitrate excretion, a metabolite of nitric oxide.[84,85] Recent preliminary studies from our laboratory also have shown an effect of nitro-L-arginine methylester on the response of aortic rings without endothelium to phenylephrine in pregnant but not nonpregnant rats. The resistance to angiotensin, norepinephrine, and vasopressin that characterizes normal pregnancy has also been shown to be reversed by the blockade of nitric oxide synthase.[86] In Figure 21 is shown the hypothesis whereby nitric oxide-induced arterial vasodilation initiates arterial underfilling in pregnancy. Moreover, endothelial damage in pregnancy, perhaps due to a circulating toxin released from an ischemic placenta, may initiate the events leading to the preeclampsia-eclampsia state.[87] These events are shown in Figure 22, including increased sensitivity to pressor hormones, a decrease in the GFR and renal blood flow, and failure to escape from the sodium-retaining effect of aldosterone, all combining to cause proteinuria, hypertension, and edema—the hallmarks of the preeclampsia-eclampsia state.[88]

In conclusion, to quote John Masefield: "What is life, the thing of watery salt held in cohesion by unresting cells which work, they know not why, which never halt myself unwitting where their master dwells." Our unifying hypothesis of body fluid volume regulation indicates that "the master" dwells in the arterial circulation.

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Epitomes

Important Advances in Clinical Medicine

Nuclear Medicine

Kenneth Lyons, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in nuclear medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Nuclear Medicine of the California Medical Association, and the summaries were prepared under the direction of Dr Lyons and the panel.

Bone Pain and Radionuclide Therapy

THERAPY FOR BONE PAIN associated with skeletal metastatic disease often presents as a challenging clinical problem. An important advance came with the recent United States Food and Drug Administration (FDA) approval of strontium 89 for the treatment of bone pain due to neoplastic disease. Strontium 89 (Metastron) is one among several agents that has received a great deal of attention in recent years as another possible therapeutic option.

β-Emitting radioactive agents have been used in the treatment or palliation of a number of diseases. In contrast to brachytherapy, β-emitters are unsealed radioactive sources given intravenously, orally, or intracavitarily. For more than 30 years, nuclear medicine has used a β-emitter, sodium iodide I 131, for the treatment of benign and malignant thyroid diseases, including hyperthyroidism and thyroid carcinoma. Radioactive phosphorus (^{32}P) has been effective for the treatment of polycythemia vera, bone metastases, and the intracavitary treatment of malignant effusion. Over the past 40 years, ^{32}P-sodium phosphate treatment of painful skeletal metastatic disease resulted in the control of symptoms in 60% to 90% of patients. This therapy is limited by its hemopoietic depression, with a decrease in leukocytes and platelets, and its being taken up by normal tissue such as the liver.

The use of strontium 89 has been highly successful for the palliative treatment of bone pain due to neoplastic disease. Minimal depression of leukocyte and platelet counts is rarely of clinical importance. The strontium 89 infusion is done as an outpatient therapy. In contrast to chemotherapy, there is no associated nausea and vomiting. Treatment can be readministered at three-month intervals. The current approach requires the recording of widespread skeletal disease by bone scintigraphy within a month of treatment. In addition, a current complete blood count is reviewed before treatment for a leukocyte count of at least 2.4×10^9 per liter (2,400 per mm^3) and a platelet count of at least 60×10^9 per liter (60,000 per mm^3).

Patients receive the infusion over several minutes and are monitored for about 20 minutes after the infusion. A patient's pain medication can be decreased an average of 50% to 60% after a successful treatment response. The response rate to strontium 89 therapy is about 76%. Because the radioactivity that is not taken up by the bone is excreted into the urine, incontinent patients must be catheterized for 72 hours following treatment.

A transient worsening of bone pain called the "flare phenomenon" occurs in about 5% of patients treated with strontium 89. Thought to be a worsening of symptoms due to a response to the strontium 89 therapy, it may occur 48 to 72 hours after the dose is given, may last for three to five days, and can be effectively treated with analgesics or corticosteroids. Newer agents, such as samarium 153 and rhenium 186, which are soon to be approved by the FDA, seem to allow concurrent treatment and bone imaging because of the favorable imaging energies not seen with the pure β-emitters such as ^{32}P or ^{89}Sr. These agents are important new adjuncts in the care of patients with painful skeletal metastatic disease.

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New Diagnostic Tests Combining Drugs and Nuclear Medicine

SEVERAL RELATIVELY NEW diagnostic applications in nuclear imaging rely on an assessment of the response to an administered drug. Cholecystokinin-augmented gallbladder scintigraphy is useful in patients with possible biliary dyskinesia who have no disease on ultrasonography and a normal-appearing gallbladder during biliary scintigraphy. Sincalide (Kinevac), a biologically active fragment of cholecystokinin, is given in a standard dose followed by dynamic imaging of the gallbladder during a nuclear biliary scan. Normally at least 40% of bile is ejected. Abnormal studies indicate a high probability of occult gallbladder disease—particularly if the pain is reproduced—and predict the relief of symptoms after cholecystectomy.

Intravenous dipyridamole (Persantine), adenosine, or dobutamine to produce stress for myocardial perfusion imaging allows the evaluation of coronary artery disease in patients who cannot perform adequate exercise because of noncardiac limitations such as orthopedic or pulmonary disease. A drug protocol is substituted for the treadmill, and myocardial perfusion imaging with thallium or sestamibi is done in the same manner as with exercise. Dipyridamole produces inhomogeneity of coronary artery flow and myocardial perfusion because it is a potent vasodilator. Fixed stenoses cannot dilate, but normal coronary arteries do. In regional coronary artery disease, a discrepancy in perfusion is mirrored by a defect on the subsequent images. Resting scans are compared to differentiate scar from viable myocardium, just as in exercise studies. Accuracy for detecting coronary artery disease is similar to that with imaging after treadmill stress, with no increase in morbidity.

In much the same way, acetazolamide (Diamox), a potent cerebral vasodilator, may be used with perfusion brain scanning to unmask cerebrovascular disease. A relatively new brain scanning tracer, technetium Tc 99m exametazine (hexamethyl-propyleneamine oxime; Ceretec), is rapidly cleared from the circulation and distributes in the brain tissue according to blood flow. With tomographic imaging, there are varied applications in neurologic disorders, particularly in cerebrovascular disease. Previous infarction of the brain causes perfusion defects that are detected much as is myocardial infarction. When acetazolamide is administered intravenously 10 to 15 minutes before the flow-directed tracer, relative inhomogeneity of cerebral blood flow is caused by the same mechanism described for the heart. This procedure has proved useful in detecting both extracranial and intracranial stenoses.

Interventional renography provides improved noninvasive diagnosis of renal artery stenosis as a cause of curable hypertension. Captopril (Capoten), an angiotensin-converting enzyme inhibitor, given orally before a standard renogram (^{99m}Tc-pentetate or ^{99m}Tc-mertiatide [TechneScan MAG 3]) reverses the compensatory effect of angiotensin that maintains glomerular filtration in renal artery stenosis, potentiating asymmetric isotope uptake. Highly specific results are obtained when the captopril study is abnormal and a baseline study (without angiotensin-converting enzyme inhibitor) is normal or less abnormal. Accuracy has approached 95% for renal artery stenosis in some studies. These results rival those with the more invasive and costly digital subtraction angiography.

Diuretic renography helps assess the functional relevance of urinary tract narrowing and the accompanying dilatation seen on both nuclear and contrast radiographic techniques. If the retention of isotope in the collecting system persists (or is increasing) late in the course of a standard renographic study, giving furosemide causes accelerated clearance in patients with functional dilatation but not in those with obstruction. Assessment by diuretic renography correlates well with the more invasive Whittaker test.

These five applications of pharmacologic intervention are readily instituted and applied in current-generation nuclear medicine departments and provide additional diagnostic information in many clinical conditions.

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Bone Imaging Using Single-Photon Emission Computed Tomography

THE UNIQUE SENSITIVITY of radioisotope bone scanning in detecting skeletal abnormalities is established, but until recently this procedure could not produce images of complex structures, such as the spine, with the anatomic clarity of newer diagnostic radiographic techniques. An advantage of computed tomography (CT) and magnetic resonance imaging (MRI) is the tomographic, or thin-section, display of results, which eliminates adjacent overlapping structures. Bone scans can now be displayed in tomographic format using gamma cameras that rotate around patients, producing thin-section images analogous to those of CT and MRI. This procedure, called single-photon emission computed tomography (SPECT), combines the high sensitivity of bone scanning with the precise anatomic localization of an abnormality.

Bone imaging using SPECT is particularly useful in patients with back, pelvic, or hip abnormalities. These patients commonly undergo scanning to discover the cause of regional pain or to evaluate the importance of a radiographically discovered abnormality. Bone scanning may uncover a lesion, yet diagnosis of the underlying condition may not be possible unless the abnormality is correctly localized to a specific anatomic site.

For example, bone SPECT can detect, localize, and differentiate between abnormalities in lumbar vertebral

bodies, pedicles, vertebral arches (including facet joints and pars interarticularis areas), or disc spaces. Such information results in accurately detecting and localizing fractures (differentiating vertebral body, pedicle, facet, and pars interarticularis locations), infections (including discitis), neoplasms (ranging from malignant tumors in vertebral bodies and pedicles to osteoid osteomas in lamina sites), and joint disease (distinguishing between articular facets and disc space-oriented abnormalities). The origin of pelvic pain can be localized to sacroiliac joints or hips, and for the hips, SPECT can discriminate between degenerative joint disease, avascular necrosis, tumors, inflammation, or fractures.

Bone imaging of many sites using SPECT is superior to conventional bone scanning. A normal-appearing conventional bone scan may harbor a lesion uncovered by SPECT. This tomographic technique improves diagnostic accuracy and also results in more meaningful consultations with referring physicians and diagnostic radiologists. The cost of a bone scan is generally less than that of a CT scan, but more than standard radiographs. Bone scanning using SPECT is superior to conventional radiography, and some investigators report more abnormalities shown by SPECT in patients with chronic low back pain than by CT.

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Positron Emission Tomographic Oncology

COMPUTED TOMOGRAPHY (CT) and magnetic resonance imaging (MRI) are elegant structural—that is, anatomical—imaging methods that have been used extensively in the diagnosis and staging of neoplasms and in follow-up after initial specific therapies, particularly in the posttherapy evaluation of suspected residual or recurrent neoplasm. Structural characteristics, however, are not sufficient to determine malignancy or to assess the distribution and extent of metabolically active tumor(s). Positron emission tomography (PET) is now showing its value as an imaging modality to identify the presence, extent, distribution, and metabolic character of a wide variety of neoplasms. Positron-emitting radiotracers have been synthesized and used to probe perfusion, oxygen metabolism, glucose metabolism, protein synthesis, nucleic acid metabolism, receptor concentrations, and tissue ischemia.

Of these agents, fludeoxyglucose F 18 (^{18}FDG) has become the most used PET radiotracer in both research and clinical applications. The active uptake and concentration of ^{18}FDG in neoplasms provides the positive signal for tumor identification in special scanning systems (PET scanners) capable of detecting photons from the decay of the ^{18}F isotope.

Researchers at the National Institutes of Health have shown that the amount of ^{18}FDG uptake in brain tumors is more predictive of prognosis than tumor grade or location. Initially low-grade tumors may undergo malignant degeneration that can be detected by PET, and following therapy, PET can identify sites of recurrence and distinguish these from regions of necrosis and fibrosis. Positron emission tomography is frequently used to guide biopsy studies toward the most metabolically active regions of tumors.

Head and neck tumors that are initially fairly well defined by CT and MRI may be associated with contralateral disease and ipsilateral lymph nodes smaller than 1 cm; PET can determine which of these is metabolically active. These tumors frequently recur following initial surgical therapy and subsequent radiotherapy, which produce distortions in local tissues when assessed by CT and MRI. When tumors recur, the PET signal may not be affected by the preceding treatments.

Lung cancers have been accurately diagnosed and staged with PET, which according to published reports has sensitivities and specificities in excess of 90% for diagnosing solitary pulmonary nodules and staging the mediastinum. Published data suggest that CT has limited sensitivity and specificity for diagnosing and staging lung cancers. If used in the initial evaluation of solitary pulmonary nodules, PET may reduce the number of thoracotomies that are being done for benign solitary pulmonary nodules as well as complications associated with transthoracic needle biopsies and thoracotomies. A prospective multi-institutional study of solitary pulmonary nodules will be completed before the end of 1994. Similar efforts are under way with breast and colorectal cancers. A recently published study on a series of patients with ovarian carcinoma reported that PET has greater positive and negative predictive values than CT for diagnosing pelvic malignant neoplasms. But when PET and CT results are combined, the negative predictive value approaches 100%. This would be valuable in avoiding second-look operations.

Other settings where PET has proved useful are in evaluating the site and extent of residual or recurrent thyroid cancer, distinguishing carcinoma of the pancreas from chronic pancreatitis and bone metastasis from benign bone fractures, and identifying malignant transformation in initially benign lesions. Whole-body PET scans can frequently locate an occult primary while assessing the extent of associated metastases. Some infections, however, can produce a positive ^{18}FDG uptake and therefore could lead to false-positive results.

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Monoclonal Antibody Imaging of Colorectal and Ovarian Cancer

A MONOCLONAL ANTIBODY labeled with indium 111, satumomab pendetide (OncoScint CR/OV), was recently approved by the United States Food and Drug Administration and now is routinely available for the imaging of colorectal and recurrent ovarian cancers. The radiopharmaceutical is given intravenously, and imaging is done within three to five days.

OncoScint CR/OV is more sensitive than computed tomography (CT) for the detection of cancer in the pelvis (OncoScint CR/OV 74%, CT 57%), mesentery, and retroperitoneum (OncoScint CR/OV 66%, CT 34%), but less sensitive in the liver (41% versus 84%). It can detect metastatic disease in normal-sized lymph nodes and can distinguish between scar tissue and recurrent cancer. The positive predictive value of OncoScint CR/OV is 97% for colorectal cancer and 83% for recurrent ovarian cancer. Consequently, a focus of uptake usually indicates disease. The negative predictive value, however, is only 19% and 29%, respectively, so a normal scan does not rule out recurrent disease.

When used appropriately, OncoScint CR/OV can be both clinically efficacious and cost-effective. Its use can cause a false-positive elevation in carcinoembryonic antigen levels for several months, however. The $2,000 evaluation can help avoid even higher costs and influence patient management in the following four clinical settings:

- Patients with a previous history of colorectal or ovarian cancer who present with an elevated carcinoembryonic antigen or CA 125 level are at high risk for recurrent disease. In this setting CT, magnetic resonance imaging, and ultrasonography show low sensitivity and specificity. OncoScint CR/OV may identify the site of recurrence and enable earlier surgical intervention.
- Patients with "resectable" recurrence of colorectal cancer (such as a solitary liver metastasis) may be candidates for surgical resection with curative intent. If OncoScint CR/OV imaging before surgical therapy identifies unexpected nonresectable disease elsewhere, a futile operation may be avoided.
- Following resection and chemotherapy, cases of ovarian cancer are often restaged surgically because of a lack of an accurate imaging procedure for detecting residual disease. In these patients, abnormal uptake on OncoScint CR/OV imaging may make a second-look laparotomy unnecessary, or the scan can be used to direct a limited laparoscopic procedure for tissue confirmation. Because of its poor negative predictive value, however, a normal OncoScint CR/OV scan does not eliminate the need for laparotomy.
- In patients with suspected recurrence following surgical or radiation therapy for rectal cancer, CT and magnetic resonance imaging are often unable to distinguish between scar tissue and recurrent disease. OncoScint CR/OV imaging in these patients is often definitive, and the scan findings may be used to determine if palliative or possibly curative therapy is warranted.

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Regional Cerebral Blood Flow and Cocaine Abuse

COCAINE ABUSE is a major and costly problem. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are windows into brain function. In the past decade, they have provided information about the acute and chronic effects of cocaine abuse. An aim of diagnostic imaging is to distinguish typical changes of cocaine abuse from those of other conditions. Identifying the presence of cocaine abuse will permit appropriate treatment.

Cerebral blood flow and metabolism in patients who abuse cocaine vary with the duration of withdrawal. Within a day of their last ingestion, these patients have lower than normal flow to anterior cortical areas on PET scans using oxygen 15. After seven to ten days, blood flow to the left dorsolateral prefrontal cortex continues to be decreased in most of these patients. In contrast, global brain metabolism is above normal in these patients after a week off cocaine, with regional increases in the basal ganglia and orbitofrontal cortex. The dorsolateral prefrontal cortex directs executive brain function, whereas the orbital cortex is associated with compulsive behaviors. Both receive dopaminergic innervation from the ventral tegmental area. Longer intervals off cocaine produce minimal additional changes, with persistent cerebral blood flow decreases in the dorsolateral frontal cortex on both sides and in the right parietal cortex. In a sagittal projection, blood flow deficits produce a scalloped pattern in the frontal and parietal lobes. After as long as six months of abstinence, the metabolic and cerebral blood flow deficits failed to reduce, suggesting that cocaine-induced changes are long term and may be permanent. We have recently compared 15 nonpsychotic persons with cocaine abuse with 13 control subjects using technetium Tc 99m exametazime (hexamethyl-propyleneamine oxime). Patients were drug-free for an average of 12 days before the study. In agreement with other studies, we found that those who abuse cocaine

had below-normal cerebral blood flow in the dorsolateral prefrontal, dorsomedial, and orbitofrontal cortex.

Cocaine abuse can lead to a paranoid psychotic state that is clinically indistinguishable from schizophrenia. Thus, persons who abuse this drug often are diagnosed with schizophrenia after several cocaine-induced episodes of psychosis. The differential diagnosis of the two conditions usually rests on the accuracy of the historical information from a psychiatric interview or on the findings of toxicologic screens of body fluids. If the patient has recurrent cocaine-associated psychotic episodes, the clinical distinction becomes even murkier. Years of cocaine abuse, unemployment, and homelessness can erode the basic personal and social capacities of a person, much like chronic schizophrenia does. Positron emission tomography or SPECT scans may help to differentiate between these two groups. Both groups show decreased flow (and metabolism) in frontal lobes and changes in caudate nuclei, but withdrawal leads to a return to normal basal ganglia metabolism in nonpsychotic persons who abuse cocaine. Both increased basal ganglia metabolism and drug abuse predict a poor response of schizophrenic symptoms to medication.

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Technetium Tc 99m Sestamibi for Parathyroid Imaging

TECHNETIUM Tc 99m sestamibi is a safe, nontoxic radiopharmaceutical that is commonly used for myocardial perfusion imaging. It was first used for parathyroid imaging in 1989. Technetium Tc 99m pertechnetate and thallous chloride Tl 201 had been used previously, but were not optimum because of the low count rate from thallium and the necessity of subtraction of the ^{201}Tl-chloride images from the ^{99m}Tc-pertechnetate images. False-negative and false-positive scans were also common. In the past few years, several groups have recommended the use of ^{99m}Tc-sestamibi as a replacement for the ^{99m}Tc-pertechnetate and ^{201}Tl-chloride combination.

The mechanism of the uptake in parathyroid adenomas and hyperplastic parathyroid glands has not been elucidated. Mechanisms may be similar to those of ^{201}Tl, namely the presence of a higher number of mitochondria in the oxyphil cells in these pathologic states than in a normal gland. Other possibilities are increased blood flow and potassium turnover.

The technique for imaging is simple and requires only the standard doses used for myocardial imaging, 10 to 30 mCi (370 to 1,110 MBq). The larger dose is preferable because it facilitates imaging in a shorter time and permits the use of single-photon emission tomography (SPECT). Imaging begins a few minutes after ^{99m}Tc-sestamibi is administered. Pinhole imaging is used in the neck because it provides greater detail. Additional imaging is done with routine techniques and includes the anterior neck area, right and left anterior oblique, and posterior views of the chest. Imaging of the neck is repeated with the pinhole technique and views of the chest and neck are obtained with a standard technique at two hours. The delayed images will often result in much better delineation of the abnormal hyperfunctioning gland(s) because the original activity in the thyroid gland will wash out with time, but the abnormal parathyroid gland retains the activity. The immediate images are useful because they define the thyroid and parathyroid gland anatomic relationship.

Experience has shown the test to have a sensitivity of 86% (31/36 patients) and a specificity of 100% (14 normal parathyroid glands). Adenomas can be found with a sensitivity of 96% (25/26). In the critical area of re-exploration for persistent or recurrent hyperparathyroidism, the technique is of particular importance because of the greater likelihood of finding the abnormal gland(s) in an ectopic location. Mediastinal parathyroid glands as small as 0.9 by 0.6 by 0.5 cm have been clearly delineated, and with SPECT, better localization has been achieved. In patients on suppressive thyroid therapy the ^{99m}Tc-sestamibi is not taken up by the thyroid, and the abnormal parathyroid gland tends to stand out. Because of the loss of the thyroid structure, localization may be more difficult. This technique has not been studied systematically to determine the usefulness of suppressive doses of thyroid. Patients with thyroid adenomas tend to have take-up of ^{99m}Tc-sestamibi on the early images, which clears on the delayed images. The presence of hypocalcemia might also increase ^{99m}Tc-sestamibi uptake.

^{99m}Tc-Sestamibi is now the agent of choice for the evaluation of patients with persistent and current hyperparathyroidism and should supplant the ^{99m}Tc-^{201}Tl technique.

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Alerts, Notices, and Case Reports

Mycobacterium avium-intracellulare and Acute Abdominal Pain

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ABDOMINAL SYMPTOMS are common in patients with the acquired immunodeficiency syndrome (AIDS), although surgical intervention is rarely required.[1] As the number of patients with AIDS increases, surgeons are increasingly asked to consider surgical exploration in AIDS patients with acute abdominal symptoms. Given the expanded differential diagnosis of acute abdominal pain and the infrequent need for surgical exploration, a reassessment of the indications for surgical exploration for specific opportunistic conditions is needed.

We report the case of a patient with AIDS and known disseminated *Mycobacterium avium-intracellulare* (MAI) who presented with signs and symptoms of severe peritonitis; on celiotomy he had a benign-appearing peritoneum and no evidence of perforation. We suggest that MAI enteritis with mesenteric adenitis was the cause of his symptoms and that celiotomy was of no therapeutic benefit to this patient. We examine the role of this organism in acute abdominal pain in patients with AIDS and discuss the possible management options and pertinent literature.

Report of a Case

The patient, a 32-year-old man with class IV AIDS, presented to the Harborview Medical Center (Seattle, Washington) Emergency Department with a history of an acute exacerbation of his chronic, intermittent abdominal pain. He said that the pain had been present for a year and relatively unchanged for the month before presentation. He reported a 27-kg (60-lb) weight loss over the previous year that was attributed to anorexia and intermittent diarrhea due to disseminated MAI. He had been extensively evaluated with abdominal plain films, abdominal computed tomography, colonoscopy, upper gastrointestinal series with small bowel follow-through, esophagogastroduodenoscopy, and abdominal ultrasonography. All were nondiagnostic except for a colon mucosal biopsy five months previously that revealed cytomegalovirus (CMV) colonization. Concurrent blood cultures grew MAI. He was treated with rifampin, ciprofloxacin, erythromycin, and clarithromycin. He was lost to follow-up for four months and then was admitted to the medicine service for the evaluation of diffuse abdominal pain, diarrhea, and weight loss. His stool was negative for ova and parasites and fecal leukocytes. The patient's symptoms abated with conservative therapy, and he was discharged to home.

Later that same day the patient returned with the abrupt onset of excruciating abdominal pain in the absence of nausea, vomiting, melena, hematochezia, or diarrhea. His heart rate was 144 beats per minute, blood pressure 92/50 mm of mercury, and temperature 37.6°C (99.7°F). On examination he had a flat, rigid abdomen with guarding, diffuse tenderness, and rebound tenderness, especially in the left upper quadrant. His leukocyte count was 13.1×10^9 per liter, and the serum amylase level was 240 U per liter (131 Somogyi units per dl); his laboratory values were otherwise within normal limits. Plain films of the abdomen and chest did not reveal free intraperitoneal air. There was no pneumatosis intestinalis or air-fluid levels. Gas was present throughout the bowel and colon. He was assessed as having peritonitis, perhaps due to a perforated viscus from CMV or MAI enteritis, and taken to the operating room for an exploratory celiotomy.

At celiotomy the abdomen was benign appearing, with no evidence of exudate or peritonitis, ascites, or perforation. There was prominent mesenteric lymphadenopathy, most notable in the proximal jejunum. Several irregularly shaped nodules were found in the spleen and were biopsied. The liver was enlarged but normal in color and texture, and a wedge biopsy specimen was obtained. The stomach, duodenum, small and large bowel, gallbladder, and kidneys were normal in appearance and to palpation. The pancreas was slightly edematous, but did not appear inflamed.

Microscopic evaluation of the mesenteric lymph nodes showed total obliteration of nodal architecture by a diffuse histiocytic infiltrate with areas of microabscess formation, cystic dilation, and fibrosis. Stains for acid-fast bacteria revealed numerous organisms consistent with MAI and no evidence of fungal organisms or malignancy. Splenic biopsies showed focal areas of acid-fast bacteria, also consistent with MAI. The results of a liver biopsy were nondiagnostic.

After the operation the patient had a superficial wound infection and a prolonged postoperative course. He was discharged on postoperative day 10 and died shortly thereafter in hospice care.

Discussion

The differential diagnosis of acute abdominal pain in patients with AIDS must include both AIDS-related and non-AIDS-related disorders. Diffuse abdominal pain due to AIDS-related disorders can be caused by a variety of

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
MAI = *Mycobacterium avium-intracellulare*

infectious diseases, including bacterial infections, cytomegalovirus, toxoplasmosis, *Candida*, histoplasmosis, atypical mycobacteria, and amebiasis, as well as neoplasms such as Kaposi's sarcoma and gastrointestinal lymphoma.[2] Peritonitis due to intestinal perforation can result from infections with opportunistic pathogens, including CMV, coccidioidomycosis, toxoplasmosis, and histoplasmosis.[3-7] In patients with peritonitis due to perforation, CMV is frequently found. Furthermore, severe spontaneous CMV peritonitis can occur in the absence of perforation, making the evaluation from a surgeon's perspective even more challenging.[8]

There is a high 30-day postoperative mortality of emergency and elective operations in patients with AIDS, reported as 57% and 43%, respectively, in one series.[9] Because of the widely expanded list of infectious and malignant causes of acute abdominal pain, the high 30-day operative mortality, and the decreased likelihood that a celiotomy will lead to beneficial therapeutic interventions, some authors have cautioned that every effort should be made to avoid celiotomy in patients with AIDS who have acute abdominal pain.[10] Our review of the literature suggests that this is especially prudent regarding patients with MAI enteritis.

Disseminated MAI was exceedingly rare before the early 1980s. Increasing reports of death from the disease emerged at the time of the original discovery of the human immunodeficiency virus.[11,12] Currently it is one of the most common systemic bacterial infections in patients with AIDS.[13,14] In a recent study of AIDS patients from Memorial Sloan-Kettering Cancer Center (New York City), disseminated MAI was found in 18.3%.[15] *Mycobacterium avium-intracellulare* can be recovered from the lungs, spleen, lymph nodes, liver, bowel, adrenal glands, and brain of infected patients.[11] Blood cultures are almost always positive for the organism in patients with this infection, as are cultures of bone marrow, liver, and lymph nodes.[15] Because of the chronic nature of the opportunistic infections in patients with AIDS, many have had multiple investigations for chronic abdominal pain and diarrhea (as in this patient), and the presence of disseminated MAI may be known before the onset of acute abdominal pain.

The role of infection with this organism in the development of diffuse abdominal pain is unclear.[16] We think that MAI mesenteric lymphadenitis can cause a clinical syndrome suggestive of diffuse peritonitis. In 35 AIDS patients undergoing celiotomy at Harbor-UCLA Medical Center (Los Angeles, California), no peritonitis was found in 2 patients explored for acute abdominal pain.[17] Both patients had enlarged lymph nodes due to MAI, suggesting that the adenitis and adenopathy may have been responsible for the acute abdominal pain. When emergency laparotomies in patients with AIDS were reviewed, it was found that 4 of 28 patients had MAI.[10] All four were systemically ill with findings of enlarged mesenteric lymph nodes on exploration. This prompted speculation that the preoperative knowledge of enteritis due to this organism might have led to the avoidance of a celiotomy in these patients. In another report of a series of five patients with AIDS who required emergency celiotomy, three had evidence of MAI. Two had massive adenopathy without evidence of perforation. In one patient, who later had disseminated MAI, a 3-mm perforation was found, raising the possibility that the organism can cause intestinal perforation in some cases.[16] In the San Francisco (California) General Hospital Medical Center experience, however, a review of all autopsy reports since 1981 failed to identify any cases of peritonitis resulting from MAI.[8]

These reports, as well as our experience, suggest that this group of patients, if identified preoperatively, may benefit from a less aggressive approach. Given the prevalence of MAI in patients with AIDS and the obvious disadvantages of doing a nontherapeutic celiotomy on patients in the end stage of their disease, a less invasive form of exploration may be beneficial to exclude surgical disease. We propose that these patients undergo a laparoscopic exploration to evaluate their acute abdominal pain. Laparoscopic exploration provides a means of evaluating acute abdominal pain in patients with AIDS that results in far less disability and postoperative pain. The exclusionary role of an abdominal exploration can be accomplished, and when indicated, a laparoscopy can be converted to an open procedure. Further study is needed to assess the efficacy of this procedure for evaluating acute abdominal pain in patients with AIDS.

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Lactic Acidosis in a Patient With Multiple Myeloma

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TYPE B LACTIC ACIDOSIS has been described in association with a variety of hematologic malignant neoplasms and solid tumors. We report the first case of type B lactic acidosis occurring in a patient with multiple myeloma. We also review functional abnormalities relevant to the genesis of lactic acidosis in patients with malignancy and those with multiple myeloma.

Report of a Case

The patient, a 60-year-old woman, was admitted because of vomiting and weakness for four days. She had had multiple myeloma for three years with diffuse lytic lesions in the humerus, skull, and thoracic spine. She received radiation therapy (50 Gy [5,000 rads]) in February 1993 for spinal cord compression and received additional courses of radiation therapy in July 1993. She had also been treated with several cycles of chemotherapy consisting of melphalan, cyclophosphamide, and prednisone. Her myeloma was deemed to be unresponsive to therapy. Outpatient medications included acetaminophen, dexamethasone sulfate, fluconazole, and sulfamethoxazole.

On admission the patient appeared nontoxic. Her blood pressure was 170/82 mm of mercury, her heart rate was 120 beats per minute, respirations were 20 per minute, and her temperature was 36.9°C (98.5°F). Her mucous membranes were dry. Nodules were noted over the skull diffusely. Pain was elicited to palpation of the left upper chest wall. The results of the physical examination were otherwise unremarkable. Admitting laboratory test values included the following: leukocyte count 10.7 $\times 10^9$ per liter (10,700 per mm^3), hemoglobin 115 grams per liter (11.5 grams per dl), and platelet count 229 $\times 10^9$ per liter (229,000 per mm^3). Serum sodium level was 137 mmol per liter (137 mEq per liter), potassium 5.1 mmol per liter (5.1 mEq per liter), chloride 104 mmol per liter (104 mEq per liter), carbon dioxide 12 mmol per liter (12 mEq per liter), anion gap 21, total calcium 6.1 mmol per liter (12.3 mEq per liter), urea nitrogen 15.4 mmol per liter (43 mg per dl), creatinine 88 µmol per liter (1.0 mg per dl), and glucose 6.2 mmol per liter (112 mg per dl). Liver function test values were normal. A prothrombin time was 11.2 seconds. Arterial blood gas determinations with the patient breathing room air were as follows: pH 7.35, P_{CO_2} 20 mm of mercury, P_{O_2} 100 mm of mercury, bicarbonate 10.8 mmol per liter (10.8 mEq per liter), and arterial oxygen saturation 95%. An arterial lactate level was 8.5 mmol per liter. A urinalysis was normal. The chest x-ray film showed a small left pleural effusion. Gram's stain of a sputum specimen was unremarkable.

The cause of the increase in lactate was not obvious. The patient was never observed to have seizure activity. The presence of occult tissue hypoperfusion was considered, and intravenous fluids were administered. In addition, a regimen of broad-spectrum antibiotics was started empirically for possible sepsis. When the elevated blood lactate level did not diminish with hydration, a pulmonary artery catheter was inserted to further define the perfusion status. The cardiac output was 8.7 liters per minute, the systemic vascular resistance was 746 dynes • second • cm^{-5}, the pulmonary artery pressure was 28/4 mm of mercury, the pulmonary artery wedge pressure was 9 mm of mercury, right atrial pressure was 6 mm of mercury, mixed venous oxygen tension was 42.4 mm of mercury, percentage of saturated venous oxygen was 78.6%, oxygen extraction ratio was 0.2, and the lactate level was 6.6 mmol per liter. A course of thiamine was empirically administered but had no effect on the lactate level. The patient remained afebrile; the leukocyte count ranged from 5.3 to 10 $\times 10^9$ per liter. Antibiotic therapy was stopped after eight days. Culture of urine, blood, and sputum specimens was negative for pathogens. The blood lactate concentration continued to be elevated throughout her hospital course and was 9.5 mmol per liter at the time of her discharge from hospital. Radiation therapy was planned on an outpatient basis. She was readmitted three weeks later with recurrent hypercalcemia and weakness, and her blood lactate concentration remained elevated throughout this admission. She was discharged home on a regimen of calcitonin.

Discussion

The most common cause of lactic acidosis in patients with malignant neoplasms is tissue hypoperfusion due to hypovolemia, sepsis, or cardiac dysfunction.[1] Lactic acidosis occurring in patients with clinical evidence of poor tissue perfusion or oxygenation (such as hypotension, cyanosis, cool extremities) is classified in the Cohen and Woods system as type A lactic acidosis.[2] Tissue hypoperfusion was thought not to be present in our patient based on the normal hemodynamic profile, negative cultures, and persistent lactic acidosis at the time of discharge.

(Mizock BA, Glass JN: Lactic acidosis in a patient with multiple myeloma. West J Med 1994; 161:417-418)

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It was first noted in 1961 that lactic acidosis could occur in patients in whom neither shock nor hypoxemia was evident.[3] Lactic acidosis that occurs without clinical evidence of tissue hypoperfusion is classified as type B.[2] In 1963 type B lactic acidosis was described in patients with acute leukemia.[4] Since then, various hematologic malignant neoplasms have been reported to cause lactic acidosis. In addition, lactic acidosis has also been noted to occur with solid tumors (breast, colon, lung), usually in the presence of liver or bone marrow metastases.[5] Type B lactic acidosis has not, to our knowledge, been previously described in patients with multiple myeloma.

Although the ultimate cause of lactic acidosis is an imbalance between lactate production and use, the mechanism in malignant disorders is controversial. Lactate production is largely determined by glycolytic activity.[6] It has been postulated that in patients with cancer, glycolytic flux is stimulated by ischemia due to a tightly packed neoplastic tissue bed or leukemic microemboli.[7] It is also possible that increased lactate production is caused by a primary increase in glycolytic activity in neoplastic tissue. The association between malignant disease and abnormalities of glucose metabolism was initially described in 1925.[8] In 1930 it was noted that malignant cells showed accelerated glycolytic activity with the production of lactic acid.[9] It was proposed that cancer cells had decreased respiration that caused the cells to increase their glycolytic rate to maintain adenosine triphosphate production. Later studies supported the observations of increased glycolytic activity but found that tissue oxygenation and respiratory activity in neoplastic cells were intact.[10] This primary increase in glycolytic activity has been called aerobic glycolysis.[10] The reason why malignant cells choose to satisfy their energy demands in this way is not clear. Glycolytic activity in cancer cells is much less responsive to feedback regulation and proceeds at a higher rate than required by the Krebs cycle.[6,9] This may confer advantage to malignant cells by promoting unrestrained growth.[10]

A human myeloma cell line was used to show that glycolytic flux and lactate production were increased by insulin and insulinlike growth factor-1 (IGF-1).[11] The ability of insulin and IGF-1 to stimulate glycolysis and lactate production in myeloma cells may relate to the fact that plasma cells are derived from the same germ layer as tissues traditionally considered to be insulin sensitive—liver, muscle, and fat.[11] It is not clear, however, why lactic acidosis has not been previously noted in patients with multiple myeloma. Possibly only rare myeloma cell lines are capable of increasing lactate production enough to overwhelm utilization pathways.

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Hemorrhagic Fever With Renal Syndrome in California

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HANTAVIRUS DISEASE (HVD) encompasses the spectrum of illness caused by infection with viruses of the *Hantavirus* genus of Bunyaviridae.[1] Antibodies to hantaviruses have been demonstrated in human serum specimens throughout the world.[2] Until recently, hantavirus infection was thought either to be asymptomatic or to result in hemorrhagic fever with renal syndrome, an illness of varying severity characterized by fever, hypotension, acute renal failure, and thrombocytopenia.[3] The recent detection in the southwestern region of the United States of rising antibody titers to hantavirus in serum specimens from persons with unexplained acute respiratory failure shows that the clinical expression of hantavirus infection is broader than originally recognized.[4] Annually there are about 200,000 documented cases of hemorrhagic fever with renal syndrome worldwide, with nearly 50% of the cases in the People's Republic of China. Fewer cases occur in Korea, Russia, Scandinavia, Europe, and the Balkan region.[2] We describe a case of this illness confirmed in a California resident with a recent history of travel to Korea.

Report of a Case

The patient, a 30-year-old Korean man, was admitted because of nausea and vomiting associated with diffuse abdominal pain, headache, nonproductive cough, myalgias, and temperatures as high as 38.3°C (101°F), all of three days' duration. Four days before admission the patient had returned from a vacation to Korea. He had trav-

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control and Prevention
ELISA = enzyme-linked immunosorbent assay
Ig = immunoglobulin

eled during the month of December 1993 and had stayed in rural inns where he at times slept on the floor.

On physical examination the patient was orthostatic to pulse only. He had mildly injected sclerae, an erythematous oropharynx, and a nondistended abdomen that was soft but diffusely tender only on palpation. A stool specimen obtained on rectal examination was brown and tested positive for occult blood. A nonpalpable petechial rash was present over the patient's legs and back.

Initial laboratory studies showed a leukocyte count of 46.8×10^9 cells per liter with a manual differential of 0.16 neutrophils, 0.44 bands, 0.08 lymphocytes, 0.05 monocytes, 0.01 eosinophils, 0.01 basophils, 0.02 metamyelocytes, 0.01 progranulocytes, and 0.22 blast forms. The platelet count was 37×10^9 per liter. The hematocrit was 0.59. Urinalysis revealed a specific gravity of 1.022, pH 5.0, 3+ protein, 1+ ketones, 0 to 3 leukocytes and erythrocytes, greater than 50 hyaline casts, and occasional granular casts with rare erythrocyte inclusions. The other abnormal admission laboratory values are shown in Table 1. Cultures of blood and urine were obtained, and a regimen of intravenous cefotetan was started empirically.

A closer review of the peripheral blood smear showed that the cells originally thought to represent blast forms were instead atypical lymphocytes. A Monospot slide test was negative for infectious mononucleosis. A test for hepatitis B surface antigen was positive. On hospital day 2 after intravenous hydration, the leukocyte count was 49.3×10^9 per liter, the hematocrit was 0.489, and the platelet count was 52×10^9 per liter. The serum creatinine level remained elevated at 210 μmol per liter (2.4 mg per dl). The patient continued to be afebrile and normotensive.

On hospital day 3 periorbital puffiness was noted on physical examination, along with bibasilar rales. An abdominal ultrasonogram showed small pleural effusions of both lungs. Furosemide was administered intravenously with subsequent moderate diuresis.

The patient's temperature went up to 38.8°C (102°F) on hospital day 4. The platelet count had risen to 135×10^9 per liter and the leukocyte count had come down to 22.8×10^9 per liter. The serum creatinine level rose to 410 μmol per liter (4.6 mg per dl). Despite escalating doses of diuretics, the urine output fell to below 500 ml per 24 hours, and the patient began to have shortness of breath. Worsening rales were noted on pulmonary examination, and the results of a chest x-ray film were consistent with pulmonary edema. Arterial blood gas determinations with the patient breathing room air revealed a pH of 7.39, Po_2 of 42 mm of mercury, Pco_2 of 29 mm of mercury, and a bicarbonate level of 17.5 mmol per liter (17.5 mEq per liter). The patient was placed on supplemental oxygen therapy. A cross-referenced MEDLINE search on thrombocytopenia, acute renal failure, and Korea suggested the diagnosis of hemorrhagic fever with renal syndrome. A serum specimen for serologic testing of antibodies to hantavirus was sent to the Centers for Disease Control and Prevention (CDC).

On hospital day 6 the patient's urine output increased to more than 3 liters per 24 hours in the absence of diuretic administration. The serum creatinine level decreased to 320 μmol per liter (3.7 mg per dl). The following morning the patient left the hospital against medical advice. That afternoon the CDC reported that the patient's serum contained immunoglobulin (Ig) M antibody against hantavirus.

At outpatient follow-up 11 days later, the patient had no complaints, his blood urea nitrogen level was 3.6 mmol per liter (10 mg per dl), and his serum creatinine level was 110 μmol per liter (1.3 mg per dl).

TABLE 1.—*Abnormal Serum Biochemistry Values on Admission*

Test, Serum	*Results*	
	SI Units	*(Conventional Units)*
Sodium, mmol/liter (mEq/liter)	125	(125)
Urea nitrogen, mmol/liter (mg/dl)	21.1	(59)
Creatinine, μmol/liter (mg/dl)	260	(2.9)
Alanine aminotransferase, U/liter (units/liter)	109	(109)
Aspartate aminotransferase, U/liter (units/liter)	119	(119)
Lactate dehydrogenase, U/liter (units/liter)	1,500	(1,500)
Creatine kinase, U/liter (units/liter)	275	(275)
Calcium, mmol/liter (mg/dl)	1.92	(7.7)
Magnesium, mmol/liter (mg/dl)	0.6	(1.4)
Amylase, U/liter (units/liter)	320	(320)

SI = Système International

Discussion

During the Korean War a syndrome of fever and acute renal insufficiency associated with thrombocytopenia and hemorrhagic manifestations of varying degree developed in more than 2,000 United Nations troops.[5] This clinical spectrum was labeled Korean hemorrhagic fever and was compared with similar syndromes reported in Scandinavian countries (nephropathia epidemica) and in China and Japan (epidemic hemorrhagic fever). It was not until 1978 that the causative agent of Korean hemorrhagic fever, Hantaan virus, was first isolated from lung tissue of a striped field mouse (*Apodemus agrarius*).[6] Subsequent research revealed that the similar clinical syndromes were caused by closely related viruses.[7,8] In 1982 a World Health Organization working group recommended that these diseases be referred to as hemorrhagic fever with renal syndrome.[9] The initial three viral strains shown to cause human disease were grouped into the *Hantavirus*

genus of the Bunyaviridae family.[2] Further serologic study has established additional hantavirus serotypes,[10] each serotype characterized by a prototypical mammalian vector, geographic distribution, and disease severity (Table 2).[11-13]

Humans become infected with hantavirus through inhalation or direct contact with virus found in rodent excreta. Hantavirus infection in rodents is unique in that despite the presence of neutralizing antibody, infectious virus continues to be secreted in urine, saliva, and feces without any detrimental effect on the host rodent.[14] Human excretion of virus is minimal, and transmission between humans has never been reported.[1] Possible hantavirus vector-rodents are widespread. Serologic evidence of hantavirus infection has been demonstrated in 81 species of animals in more than 50 countries on all continents except Antarctica.[2] In the United States the highest prevalence of hantavirus-infected rats has been found in Baltimore, Maryland (34% to 74%); New Orleans, Louisiana (31% to 41%); the Hawaiian islands (6% to 18%); and Philadelphia, Pennsylvania (12%).[10] Seroprevalence surveys of rodents in California, Alaska, Colorado, New Mexico, and Utah have found a prevalence of hantavirus infection as high as 21%.[10] Testing of rodents captured in and around homes of case-patients in the recent southwestern United States outbreak of acute adult respiratory distress syndrome revealed 32 of 107 (30%) deer mice (*Peromyscus maniculatus*) to be positive for hantavirus infection.[15] Despite the widespread distribution of infected rodents, no indigenously acquired case of hantavirus disease had been reported in the United States before the recent recognition of hantavirus-related severe respiratory illness (hantavirus pulmonary syndrome) in the southwestern United States.

The incubation period for hemorrhagic fever wth renal syndrome is generally two to three weeks, with a range of 4 to 42 days. Early symptoms include high fever, flushing of the face, myalgias, conjunctival and pharyngeal injection, frontal headache, and a petechial rash, with subsequent development of nausea and vomiting, severe abdominal pain, and back pain with costovertebral angle tenderness.[3,5,16] Hiccups and severe thirst are common.[5] The classic syndrome has five clinical stages: febrile, hypotensive, oliguric, diuretic, and convalescent. Distinct stages often are not recognizable, especially with mild to moderate disease. The febrile stage can last as long as five days. Shock and oliguric phases often overlap and last an average of six days (range 2 to 12 days). Convalescence can take months, with persistent proteinuria and defects in urine-concentrating ability.[17]

Laboratory findings invariably include proteinuria, often pronounced. As a rule, azotemia is present as well, but it may be absent in mild cases.[16] Leukocyte counts are substantially elevated, especially in Hantaan strain infections. Atypical lymphocytes on a peripheral smear are seen in more than 93% of cases, and the simultaneous presence of immature granulocytes and giant platelets supports the diagnosis of hemorrhagic fever with renal syndrome.[5]

Our patient had transient hypoxemia with radiographic evidence of pulmonary edema on days 7 and 8 of his illness. This clinical finding is particularly interesting in light of the recent descriptions of hantavirus pulmonary syndrome in the United States. Vascular endothelial cell injury followed by increased capillary permeability is thought to result in the observed pulmonary complications.[18]

TABLE 2.—*Hantavirus Genus Varieties*

Virol Serotype (Yeor Discovered)	*Acute Disease Severity*	*Seosonolity*	*Prototypicol Vector*	*Documented Distribution*
Hantaan (1976)	20% severe; 50% moderate; 30% mild	Late fall or early winter; spring or early summer	Striped field mouse (*Apodemus agrorius*)	Asia: China, Korea (rural)
Seoul (1982)	Mild to moderate; severe on occasion; hepatitis	None	Domestic rat (*Rattus rottus, Rattus norvegicus*)	Worldwide (urban)
Puumula (1984)	Less severe	Late fall or early winter; mid to late summer	Bank vole (*Clethrionomys gloriolus*)	Scandinavia, Russia, Europe
Prospect Hill (1982)	Asymptomatic*	--	Meadow vole (*Microtus pennsylvonicus*)	Maryland, Minnesota†
Leakey (1988)	Severe‡	--	House mouse (*Mus musculus*)	Texas, Maryland, Minnesota†
Porogia (1987)§	Severe	?	?	Greece†
Belgrade (1992)‖	Severe	?	Yellow-necked mouse (*Apodemus flavicollis*)?	Balkan region†
Muerto Canyon (1993)	Severe; adult respiratory distress syndrome	Single outbreak in spring 1993	Deer mouse (*Peromyscus maniculotus*)	Concentration in southwestern United States†

* No acute symptoms documented to date.

† Actual event of geographic distribution unknown.

‡ A single case of serologic evidence of Leakey virus infection has been reported in a patient with severe hemorrhagic illness and renal insufficiency (Baek et al[11]).

§ Proposed name for hantavirus identified in a severely ill patient with hemorrhagic fever with renal syndrome in Greece that showed a unique serologic pattern relative to Hantaan, Seoul, and Puumula viruses (Antoniades et al[12]).

‖ Hantavirus strain is identified in severely ill patients with hemorrhagic fever with renal syndrome in the Balkan region (Gligic et al[13]).

The protean and nonspecific manifestations of hemorrhagic fever with renal syndrome, especially in mild to moderate cases, make diagnosing this disease on clinical grounds difficult. Important clinical clues are fever, frontal headache, and myalgias in conjunction with flushing and conjunctival or pharyngeal injection. The additional presence of hypotension, marked proteinuria, thrombocytopenia, and acute renal failure in a person with a travel history to Russia, Asia, or Scandinavia, particularly in late autumn or early winter, strongly suggests the diagnosis. A history of exposure to rodents provides collaborating evidence.

The various diseases that patients with this illness have been misdiagnosed as having include leptospirosis, scrub typhus, bacterial sepsis, dengue fever, viral hepatitis, acute surgical abdomen, and influenza. Uremia related to thrombocytopenic thrombotic purpura or the hemolytic-uremic syndrome should also be considered in the differential diagnosis. Antibiotics and nonsteroidal anti-inflammatory agents given empirically to febrile patients can result in acute renal failure due to interstitial nephritis and present a clinical syndrome suggestive of hemorrhagic fever with renal syndrome without thrombocytopenia or hypotension. Jaundice is rare in this disease, and its presence is indicative of leptospirosis or viral hepatitis. Similarly, a maculopapular rash is more consistent with leptospirosis or scrub typhus.

The current diagnostic method of choice is the detection of IgM antibodies against hantaviruses using enzyme-linked immunosorbent assay (ELISA). Testing is available through the CDC Special Pathogens Branch of the Division of Viral and Rickettsial Diseases. Although the ELISA is not able to determine the specific strain of infecting virus, it is a specific and sensitive technique for detecting acute hantavirus infection and is positive in most patients by day 3 of the febrile stage.[19] Specific viral strains can be determined by plaque-reducing neutralization assays.

Rapidly diagnosing this illness is important because a prospective, randomized, double-blind, placebo-controlled clinical trial in China has demonstrated a sevenfold decrease in mortality with the early use (within 6 days of the onset of fever) of intravenous ribavirin. The primary effect appears to be a reduction in the risk of entering the oliguric phase.[20] Intravenous ribavirin is not currently licensed for use in the United States, but has been made available through an investigational-new-drug protocol to treat patients with hantavirus pulmonary syndrome.

Severe hemorrhagic fever with renal syndrome has a mortality of 5% to 10%. As of December 31, 1993, a mortality of 60% had been reported in 53 confirmed cases of hantavirus pulmonary syndrome throughout the United States.[21] In mild to moderate cases of hantavirus disease, supportive care usually leads to full recovery, but recent data suggest that subclinical infections in the United States may lead to long-term sequelae. Seropositive inpatients in Baltimore were more likely than matched controls to have end-stage renal disease, hypertension, and stroke.[22]

The results of preliminary trials of inactivated vaccines against this disease have been encouraging,[23] and vaccinia-vectored vaccines are under development.[24] The best preventive measure at this time appears to be to avoid activities that would result in close contact with rodents or their excreta.

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Commentary

Case Report 23289 and Medical Economics

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Annie McDonald was a young midwestern woman in good health. During the fall of 1907 she began to exhibit behavioral changes and fell ill. She was restless and overly active. She lost weight, and her face changed character. A mass began to develop in her neck (Figure 1).

Figure 1. — Annie (Ushold) McDonald (Case Report 23289) is shown before her surgical procedure in 1908.

She was taken to Saint Mary's Hospital in Rochester, Minnesota. A medical consultation diagnosed a goiter, and surgical removal was recommended. She returned for the operation in June 1908. The procedure was complex and accompanied by the patient's abnormally high temperature while on the operating table. The hyperthermia was finally controlled by bringing an ice bath into the operating theater and immersing the patient. Her further recovery was uneventful, and she returned in good health to her home.

A quarter century later, the patient again fell ill with symptoms of metabolic imbalance. Once the swelling began in her neck, she recognized a recurrence of the goiter. She returned to Saint Mary's Hospital, and, once again, surgical therapy was recommended. She felt fortunate to return to Dr Mayo, the surgeon for her previous operation, for care. The operation this time was uncomplicated, and she was scheduled for discharge on the sixth postoperative day.

Grandmother McDonald was a grateful patient and a generous person; however, a Scottish heritage had given her a thoughtful mind and a resolute character. Her midwestern ethic was disturbed by the recurrence of her illness and the need to undergo treatment twice for the same problem. She spoke frankly to her surgeon, "If you had done it right the first time, I would not be here now!"

Explanations were offered, but they seemed to pass her understanding. Dr Mayo paused to consider. He then offered a suggestion: "What if we charge you the same fee we charged for the first surgery?" Payment for services had not really been the concern, but this compromise was immediately recognized as a "fair" solution. The issue was settled.

Subsequently, the story was repeated to her three daughters and, ultimately, her grandson whenever there seemed to be a special need for insight in discussions of larger issues of ethic or right.

A half century later, the grandson opened an old lacquered tin box of records. Carefully laid side by side were two bills for medical services set aside in quiet testimony of that moment (Figures 2 and 3). Suddenly what had been a family lesson became reality. A simple story passed through three generations crystallized into an event of clinical compassion and economic insight.

Years after these events, the medical profession lies under siege. Despite seemingly miraculous advances in medical science, physicians suffer criticism for the care they offer. It is too expensive, and it is applied excessively. Those who use the system receive the finest care the world has ever known, but availability is selective. The product delivers, and everyone wants the service.

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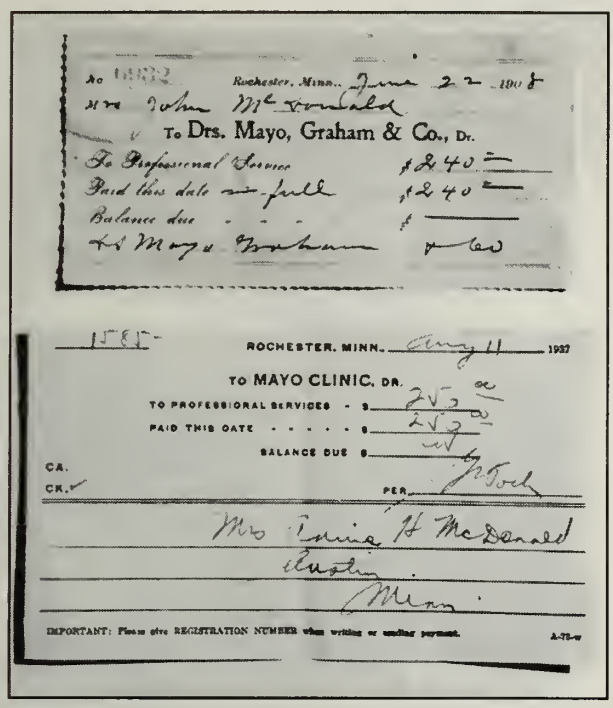

Rochester, Minn.
To Drs. Mayo, Graham & Co., Dr.
To Professional Service
Paid this date
Balance due

ROCHESTER, MINN.
TO MAYO CLINIC, DR.
TO PROFESSIONAL SERVICES
PAID THIS DATE
BALANCE DUE
CR.
CK.
PER
IMPORTANT: Please give REGISTRATION NUMBER when writing or making payment.

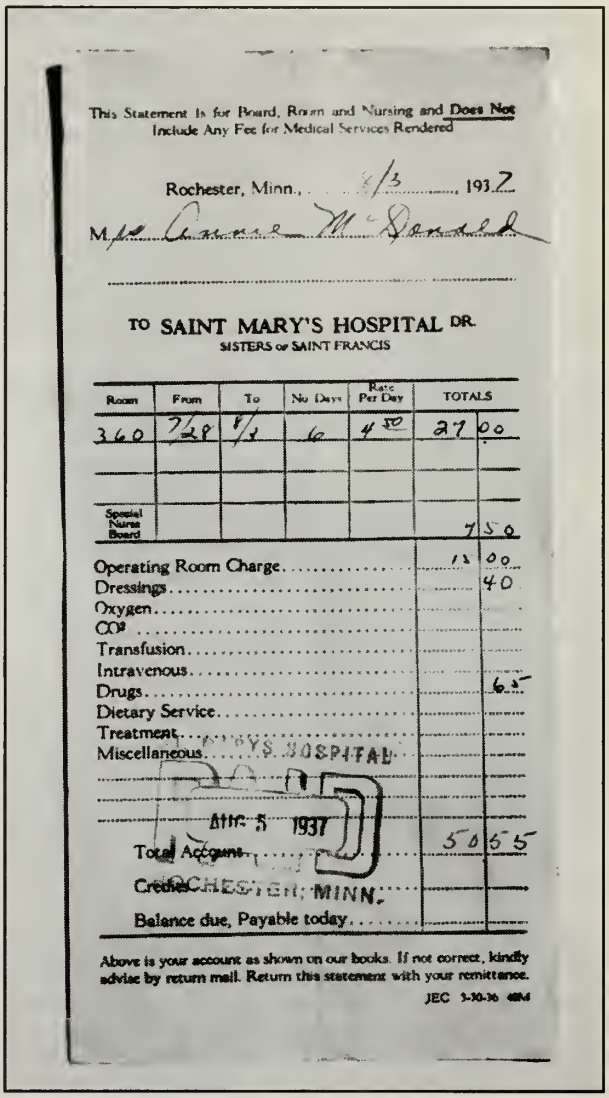
Figure 2.—Handwritten statements outline the charges for professional services in 1908 and 1937.

Only the very best will do—but our society has begun to consider whether it can afford the best.

The history of our profession and why we are here today are clear. Growth from a cottage industry of solo practitioners into large organizations within a greater health care system has paralleled the expansion of our entire nation. The need for a healthy nation, when transformed into a national right to health care, necessitated a fiscal relationship between government and medicine to deliver that promise of a healthy nation. Once patients needing care and physicians giving care had to turn to a third party to provide that care, the needs of that third party began to grow in importance. Indeed, if we "had done it right the first time," we might not be here today.

There is now another opportunity to assist our patients, to perhaps restructure our systems and restore the practice of medicine. Health care professionals remain the only group focused on the best interests of patients as the final test in debates of provided services or economic policy in medical care. We now stand between patients and those who would subordinate their needs. Here we must remain.

The task is daunting, but the effort is necessary. We must move and grow as medical practice itself evolves. The needs are many. Responsibility for health care must return in a greater way to patients. Preventive measures must accompany crisis intervention. Physicians must share increased fiscal responsibility in the care they provide. We must participate in the reformation of systems that promote cost without patient benefit. Physicians must


This Statement Is for Board, Room and Nursing and Does Not Include Any Fee for Medical Services Rendered
Rochester, Minn.,
TO SAINT MARY'S HOSPITAL DR.
SISTERS OF SAINT FRANCIS

Room	From	To	No Days	Rate Per Day	TOTALS	
360	7/28	8/3	6	4 50	27	00
Special Nurse Board					7	50

Operating Room Charge
Dressings
Oxygen
CO_2
Transfusion
Intravenous
Drugs
Dietary Service
Treatment
Miscellaneous
Total Account
Credits
Balance due, Payable today
AUG 5 1937
ROCHESTER, MINN.
Above is your account as shown on our books. If not correct, kindly advise by return mail. Return this statement with your remittance.

Figure 3.—A billing statement is shown for "Board, Room and Nursing" during a 1937 hospital stay.

be relieved of the burden of defensive medicine. Access to services must be improved. Organized medicine must become more aggressive in defending against expensive quackery. The associated vendors of medical products must be made to recognize that health services do not operate solely on a profit-incentive basis.

As physicians, we must focus on our role as patient advocates and promote what we know will be needed for the health care of our people. We must form the vanguard to lead our nation and its people to a healthy future. We must be more effective with the tools that medical science has made available to us. The science we offer must be delivered with sensitivity and skill. We must underscore the art of our practice. During these times of challenge and change when those moments arrive to consider practice or policy, perhaps we can ask, will our decisions be "fair" to Grandmother?

Commentary

Health Care Costs and Technologies

DONALD KENNEDY, PhD, *Stanford, California*

Excerpted from a speech given at a meeting of the Editorial Board of THE WESTERN JOURNAL OF MEDICINE, *May 21, 1994*

Given our level of affluence, given the kind of democracy we are, given the way we feel about people in need, what is the right amount to spend on health care? Is there, in fact, a certain normative value? Or should we let the collective but rather individual habits of the American people determine this? Because there seems to be substantial national appetite for a cure, what should be the relationship between cost and cure? What are the trade-offs? Can we save costs in a way that preserves the quality of care? Or, as we reduce costs, do we also inevitably reduce quality of care, however we define quality?

By putting the issue in the form of such questions, I hope to avoid the clutter of the current health care economics debate. Instead, I plan to classify some of the intervention strategies that we now employ in health care and look at which, if any, are responsible for the situation we have been so quick to deplore—and what effect manipulating some of them might have.

I would like to discuss three categories of interventions. The first is the set of extraordinary technologies we have developed over the past 40 or 50 years that are, everybody agrees, high-quality, life-saving interventions. They represent the peak of standards of practice in the specialties. They are expensive. They require important and costly drugs and devices. They were developed at substantial cost to the nation, as it supported the basic research establishment and as industries made substantial capital investments in them.

The justification for public support of the basic research stream that feeds these developments and for the rest of the apparatus that installs them and reimburses for them is often based on the "burden of illness" fallacy: If disease A causes x number of deaths a year and y hospital stays at z cost, we can add up the hospital and physician-payment costs and make reasonable estimates of lost work time or foregone income (the place in the economy that these persons would have occupied had they been healthy). When we have added that up, it comes to some large number like $500 million; we are then told that a successful resolution of disease A is thereby going to save the American people $500 million. Of course, it does nothing of the kind because the people who are restored to health with whatever technology we devise will, if past is prologue, get something else. The something else is likely to turn out to be more expensive to cure than the disease we already cured. We all know about the proportion of all medical expenditures that are made in the last six months of life—so "burden of illness" relief really is illusory.

Perhaps no more dramatic example exists than the sequence of interventions that have been applied in cardiac surgical and medical therapy. Coronary bypass surgery has always had some controversy attached to it, but has nevertheless been widely used and has produced dramatic improvements in the quality of life for many patients. But it was extremely expensive in terms of surgeons' fees, intensive care unit and operating room time, and all the rest. It soon developed that although it did produce dramatic improvements for some persons, they frequently had to have the operation again in five to seven years. So what one had actually done was to ratchet costs upward. Then angioplasty came along. We appeared to have on our hands a simple, much less invasive procedure that would cost only a fraction of what coronary bypass surgery costs. It was indeed an elegant development and no doubt improved the quality of life for many. Yet if we examine data on the frequency of coronary bypass surgery in the United States, not even a nick in the curve is associated with the introduction and growth of angioplasty. Persons who have angioplasty eventually have to have something else done. It may be another angioplasty or, more often, a cardiac bypass surgical procedure.

I want to call these technologies by a new name (if you have a better one, I will be glad to substitute it!): "deferral technologies." Although they accomplish wonderful things and we want to use them, they do not save costs. They actually add to them, forming an escalator that drives the economics of health care upward in a relentless fashion.

Lewis Thomas, in a brilliant assessment of medical technology, called another class of technologies "halfway technologies." They are the best we have at the moment. Often they are cumbersome and expensive. They do produce modest gains in quality but at huge

(Kennedy D: Health care costs and technologies. West J Med; 161:424-425)

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cost. They are plainly technologies on their way to being something better. Thomas's famous example was the iron lung for polio, which, of course, was replaced at a much lower cost by a vaccine.

A third class of technologies might be called "preventive technologies." They are highly effective interventions that add little cost because they are cheap themselves and because they often spare larger costs from more expensive interventions later. The kinds of things that come to mind are immunization programs against infectious diseases, accident prevention, violence prevention, and a whole array of monitoring and screening programs that attempt to identify disease early.

Now I want to pause here and promise you that this is not going to be another prevention lecture. I introduce that category only to pose what seems to me to be a fundamental question: Given our deep concern with cost, why do we not do more of the third and less of the first two? If we can have substantial improvements in quality at very little cost and so solve both of our problems with one shot, why do we not do more of it?

The reason is that many of this third class of interventions have another thing in common. They involve more or less serious intrusions into preferred modes of personal behavior. We are a highly individualistic society here in America. We resist control. Many of us have a strong preference for the present as opposed to the future. We find it difficult to defer gratification, and we operate in this country in a technology-development mode in which the primary incentives are economic ones.

These characteristics all militate against effective prevention. For example, smoking is the number one preventable public health problem in this country. Every time we suggest ways in which that particular threat could be reduced, we come across some very difficult problems. Some have to do with our hesitancy about regulation; some have to do with a certain reluctance about adding taxes. Perhaps most important of all, we run into deep difficulties because of the way people actually make their decisions. A remedy often offered for the smoking problem results from an analysis of who smokes and who does not. Smoking in this country is associated with income and education. But if you start to tease that connection apart, it turns out that education is the more robust predictor of smoking behavior—much more important than income. Indeed, the income effect is probably exerted through the education effect. I would have supposed that this occurs because people who get more education learn more about the hazards of smoking. They associate with persons who do not like to smoke and who have informative things to say about it; they therefore put out their cigarettes and vow to sin no more.

My colleague, Victor Fuchs, has taken a much closer look at this problem. He has taken a cohort of people and pushed the analysis back to when everybody had the same education level—say, age 17. You have a sample of people, all of whom have finished high school. Some will go on to college and some even to graduate school. But their smoking behavior is already established at the time they all have the same amount of education. In other words, the people who are not going to smoke are the people who are going to stay in school.

Let us not leap to the conclusion that this has to do with intelligence. (There may be some very smart people who are incapable of deferring gratification.) Fuchs thinks that it is because of a third variable, which is the source of the other two: some people simply have a different time preference than others. They are prepared to do almost anything to ensure a better future. Getting more education is part of that, and so is not smoking. This observation explains why many health behaviors tend to be associated with one another. Education, in this view, is one of a set of outcomes of a personality type or style that is capable of deferring present gratification in favor of the future.

It will be hard to design interventions that promote that kind of personal behavior. Indeed, we are experiencing contemporary lapses in prevention. Immunization has shown a disturbing trend since the early 1960s. Immunization rates for children in the United States are now poor and getting worse all the time. The rates for black children in the United States this year are the same as in Zimbabwe and Tanzania. That ought to be a source of substantial national embarrassment. But we are a nation that is unwilling to push people around a lot. In the absence of aggressive approaches—for example, a regulation that would make immunization compulsory—we have difficulty in getting such problems resolved.

Another illustration is our perplexing failure to begin to work on the most proven method for preventive treatment of viral diseases in the case of the acquired immunodeficiency virus (AIDS)—namely, the development of a killed or severely attenuated whole-virus vaccine. That is the strategy that has been successful in similar virally caused diseases. We are now spending $1.4 billion annually on AIDS research. People are arguing for more basic research and for more efforts to develop unit or recombinant vaccines based on specific antigens isolated from the AIDS virus. That is fairly sexy molecular biology, whereas developing whole-killed-virus vaccines is regarded as not terribly interesting or exciting. There also is an unwillingness on the part of government to overcome what is a clear case of market failure. You might see corporate activity in this sector if drug companies had not had a series of terrible experiences with vaccine development, both in terms of a return on investment (nobody wants to pay much for a preventive vaccine) and because of the fear of liability and the failure on the part of government to provide the necessary liability protection.

These examples illustrate a larger point. A substantial array of quality-neutral or quality-improving cost reductions would be available if only we were willing to stretch our definitions of the health care sector. If gun control were considered a public health intervention, for example, it could change a major source of mortality radically. But, like other interventions that violate our tradition of individual freedom, this one seems beyond our reach.

Editorial

Dilemma of High-Tech Care for High-Risk Patients

A PATIENT WITH alcoholism will die if a second liver transplantation is not done. An injection-drug user with a destroyed aortic valve urgently needs a prosthetic replacement. A three-pack-a-day cigarette smoker requires another angioplasty. All these patients have one thing in common—they lead high-risk lives, and they require expensive health care.

With health care expenditures in the United States moving well into a double-digit percentage of the gross national product, and with major efforts being made by the Clinton Administration to reform health care so that everyone will have basic coverage, the use of expensive technology to care for patients leading high-risk lives is becoming a real concern. Many feel that these patients do not deserve such care, while others argue that health benefits have to be equal for all.

To physicians involved in managed care who find themselves stringently overseeing the practice patterns of their colleagues to curb expenses, a patient with alcoholism who needs a liver transplant represents, in effect, "an enemy of the people." Such a patient is often perceived by physicians as an irresponsible person whose wayward lifestyle is using up medical resources that could be more satisfactorily directed toward preventive medicine, for example. Physicians therefore feel a great deal of ambivalence in using expensive therapy for such high-risk patients. For some physicians, the situation becomes so untenable that they find ways of dumping these patients into the laps of colleagues who are less judgmental.

At first glance, the concept of not rewarding "bad" behavior with medical salvation seems logical. Those who initiate trouble for themselves, like suicidal persons who shoot themselves into a morbid but not lethal vegetative state, do not appear to be "worthy" of expensive, life-prolonging care. The same might be said of injection-drug users with repeated episodes of bacterial endocarditis that totally destroyed their mitral valves. But before physicians rush to judgment and withhold care from ill-behaved persons, they should consider the busy executive who forgets to take prescribed prophylactic medicines for rheumatic heart disease, and serious sequelae develop. Or what about the bold mushroom hunters who consume the fruit of their search and have their liver destroyed by toxic mushrooms? Are they to be denied high-tech care because of their behavior? Most physicians probably would not deal harshly with them because anyone can make a mistake. Yet, persons with alcoholism or those who use illicit drugs are in trouble because they made mistakes in their choice of substances to abuse.

There are anecdotes about physicians who refuse to perform coronary artery bypass procedures on heavy smokers who will not quit their habit. Some physicians have policies that they will not care for anyone who smokes. They argue that their withholding of medical services will stimulate patients to change their bad behavior into good, thus helping to ensure better medical results for these patients. Are they adopting this approach to punish noncompliant patients?

The ethical behavior of physicians is not codified, but generally can be distilled into "First, do no harm" and "Offer whatever is needed to benefit the patient." Arbitrarily excluding patients from appropriate care because of their lifestyle is probably not concordant with the Hippocratic Oath. Yet arguments can be made that modern science and technology have put such extraordinary burdens on society's resources that the oath is no longer relevant and factors like inappropriate behavior or noncompliance have to be considered.

As each new scientific breakthrough raises the expectations of society, the possibility that patients will clamor for and receive these new therapeutic modalities is likely. That these might then be sought for high-risk persons is also possible. Because almost all new procedures and pharmacologic agents tend to be more expensive than those they supersede, making them available to all could increase the costs of health care enormously.

So far there is no "health czar" to say no when demands for new scientific achievements are made. There are, however, individual physicians who can appreciate the futility of offering expensive new treatments to patients who will not be compliant, and these physicians will say no. Others will simply go along and provide care that is doomed to failure. It could be argued that because the government often is "the payer of last resort," the government should be denying care to high-risk patients. But government is accountable to society, and it is finally society that determines whether high-risk patients deserve high-tech care.

With the tightening of health care resources, medicine, government, and society will have to accept the necessity of making unpleasant decisions, particularly those regarding the withholding of treatment from high-risk patients. Physicians will not relish being in the highly visible front lines and making draconian decisions, and they will probably cast about for others to do this unpleasant work for them. But technology grows more sophisticated each day, and each day the need to choose the appropriate algorithm for the care of high-risk patients grows more critical. None of us can hide from this reality.

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Laparoscopic Colectomy—An Initial Experience

To the Editor: Using a laparoscope to remove intra-abdominal organs has become increasingly popular in recent years. Laparoscopic removal of gallbladders has proved to be efficacious, although at some increased risk of morbidity.[1] Several authors have suggested that laparoscopy might also be used to remove segments of the colon.[2-4] We would like to share with your readers our initial experience with a consecutive and prospectively evaluated series of colon resections considered for laparoscopic resection. This evaluation was to determine the safety and frequency of this new technique in a routine surgical practice.

A total of 115 consecutive patients requiring colectomy were evaluated for the appropriateness of laparoscopic colectomy. If a patient was actively bleeding, had a colovesical fistula, or required a coloanal or ileoanal anastomosis, the patient was not considered an appropriate candidate for laparoscopic resection. By these criteria, 56 patients were judged inappropriate and 59 had attempted laparoscopic colectomy. Of the attempted procedures, 35 were completed. Laparoscopic resection was abandoned if the exposure was inadequate or if the procedure would be unduly prolonged by this technique. Among the 35 successfully treated patients, estimated blood loss was 184 ml, patients were eating at 1.1 days after the operation, narcotics were required for 1.7 days, and patients were discharged 3.7 days after laparoscopic colectomy. Complications included three cases of postoperative wound infection, one patient with intraoperative bleeding, and one with an anastomotic leak.

These data compare favorably with those of traditional techniques in terms of length of hospital stay. Substantial cost savings may be possible in those operations that are completed laparoscopically. We also learned that this procedure can be done in a reasonable period of time. In addition, we believe that the requirements for pain medication are decreased.

This experience is preliminary, and long-term follow-up is necessary to assess the adequacy of cancer resection and the incidence of long-term complications. At this point, however, it appears that in selected patients, laparoscopic removal of portions of the colon offers practical advantages to patients.

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Recurrent Hyperthermia Due to Lovastatin

To the Editor: Lovastatin, an inhibitor of hydroxymethylglutaryl coenzyme A (HMG-CoA), is a well-tolerated and effective treatment of hypercholesterolemia. Commonly reported adverse reactions include asymptomatic elevations of aminotransferase values, gastrointestinal disturbances, headache, myalgia, and rash.[1,2] We report a case of a patient with recurrent episodes of hyperthermia due to lovastatin therapy.

Report of a Case

The patient, a 55-year-old woman with Parkinson's disease, rheumatoid arthritis, hypothyroidism, and hypercholesterolemia, was admitted to Loma Linda (California) University Medical Center with a temperature of 40.5° C. She presented after two weeks of low-grade fevers treated with oral erythromycin. She was also taking furosemide, a combination drug containing levodopa and carbidopa, levothyroxene sodium, and lovastatin. She was somnolent, responded to deep pain with purposeful movements, and had cogwheel rigidity. Laboratory tests elicited the following values: serum sodium, 120 mmol per liter; potassium, 3.0 mmol per liter; chloride, 92 mmol per liter; and bicarbonate, 30 mmol per liter. A complete blood count and coagulation profile, including platelets, were normal. Cultures of blood, urine, sputum, and cerebrospinal fluid specimens were negative for pathogens. A serum thyroid-stimulating hormone level was normal. Chest radiography and computed tomography of the head were normal.

Therapy with furosemide, erythromycin, and lovastatin was discontinued. Potassium chloride and a saline solution were administered. After 48 hours her fever resolved, her mental state was normal, and electrolytes returned to normal. Three months later she was seen with an identical historical, physical, and metabolic profile treated with ofloxacin. An antinuclear antibody titer was 1:64 and a Westergren sedimentation rate was 39 mm per hour. Therapy with ofloxacin and lovastatin was discontinued. After 48 hours, her mental state returned to normal and her fever resolved. A month later she was seen a third time with the same findings. Serial cardiac enzyme levels had a normal MB fraction, but her total creatinine kinase value was elevated at 543 units per liter. The lovastatin therapy was again discontinued. After 72 hours, her fever again resolved and her mental state became normal. In the first 12 months with discontinuation of the lovastatin, she has had no further hyperthermic episodes.

Discussion

Inhibitors of HMG-CoA are widely used for the treatment of hypercholesterolemia. Lovastatin has been available in the United States since 1987, and its safety and efficacy have been well established in both short- and long-term use.[3] Although fever has been reported in a few

cases with drugs in the HMG-CoA reductase inhibitor class,[4] there are no reports of severe hyperthermia. Myopathy, rhabdomyolysis, and other serious side effects are also known to occur with the use of lovastatin.[3,5,6] This patient's response to repeated challenges with lovastatin suggest a cause-and-effect relationship. Physicians should be aware of hyperthermia as a possible side effect of lovastatin use.

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Rochalimaea—A Cosmopolitan Zoonosis?

To the Editor: A possible hazard to immunosuppressed patients from cats infected with *Bartonella henselae* (formerly *Rochalimaea henselae*)[1,2] has been described in northern California.[3-5] Amid speculation that this risk may be cosmopolitan, we sampled a similar feline population to determine prevalence in southern California, where the climate and demographics are much different.

A total of 61 domestic cats from San Diego urban and rural environs were tested in accordance with existing animal control regulations. Blood specimens for culture were obtained using pediatric lysis centrifugation tubes after the method of Koehler and colleagues.[4] Our sample consisted of 26 household pets and 35 strays.

After three weeks, 15 of 61 blood cultures (25%) grew *B henselae* (positive by polymerase chain reaction, primers directed toward B-cell trophic receptors; J.K. Steele, PhD, Engene Biotechnologies, San Diego, California, oral communication, June 1994). Younger cats were more likely than older cats to have a positive culture (9 were estimated to be younger than 2 years, with only 1 older than 5 years). The difference in prevalence from that described in northern California (25 of 61 cultures positive, 41%) was not significant ($P = .09$).

Our findings agree with those of the San Francisco investigators and suggest that *B henselae* bacteremia is a frequent (if not ubiquitous) feature of domestic cat populations. Patients infected with the human immunodeficiency virus and with other immunosuppression should be apprised of the possible hazard of bacillary angiomatosis and cat-scratch disease from cats infected with *B henselae*.

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Communicating With Patients

To the Editor: Kenneth De Ville, PhD, JD, says that the law should not get in the way of ethical physician-patient interactions.[1] I agree. But before we ask our attorneys for advice and before we involve the hospital ethics committees, we ought to pause to practice medicine using effective communication techniques with our patients. I suspect that 90% of the ethical dilemmas and legal issues we discuss in our literature would evaporate if we communicated effectively with patients.

De Ville postulates a conflict between physician and patient when the patient, a pregnant woman with a small pelvis and a large fetus, refuses a cesarean section. Why does she refuse? We do not know. Does she understand our dilemma? Probably not. So we need to discover more about her—her fears, her understanding of the effects of cesarean section, her worries about not being a good enough mother if she does not deliver vaginally, and so forth. We need to ask. And we have to explain our puzzlement and predicament.Those two procedures—discovering meaning and acknowledging our difficulties—are central to dealing with difficult physician-patient relationships.

A curious and patient physician could probably discover what a patient's difficulty is—what is getting in the way of accepting the physician's recommendation. And expressing the physician's difficulty to the patient allows the patient to see both sides more easily.

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Lessons From the Practice

Who's in Charge Here, Anyway?

ROLLIN ODELL Jr, MD, *Orinda, California*

Health care economists and other medical care experts—including some physicians—seem to assume that patients are the passive recipients of interventions and play little or no role in the clinical course of their illness, including the outcome. Bedside experience indicates otherwise.

As a freshly minted physician over 20 years ago, I shared some of the characteristics of a freshly minted coin—a shiny, unmarked face and somewhat rough around the edges. I thought I should be in charge of the medical care given to my patients, and like many of my equally young colleagues, I was sure I had all the right answers.

It did not take long before that certainty was challenged. After I had been in practice about a year, Marion was referred to me. Marion was 45 years old and had a biopsy-proven diagnosis of stomach cancer. Her prognosis was not good, but she had none of the symptoms of advanced disease. She had refused resection, and her physician had sent her to me to "see what you could do." After reviewing the clinical record and examining her, I formed an impression of a very self-determined woman. Marion had lived most of her life on a working cattle ranch near Butte, Montana. She evinced a no-nonsense, direct manner. During the initial interview she was pleasant and cooperative, but I could tell she was not about to take guff from anyone.

I explained to her that anything I could do would be strictly palliative. An operation would be effective only in reducing the bulk of her disease, and radiation treatment or chemotherapy would do the same, but the chance that we could rid her body of all the disease was remote. Her eyes hardened. "What you're trying to tell me is that it is up to me, is that right?"

I shrugged, squirmed a little in my seat, and mumbled something like, "That's about the size of it." I then launched into a description of various treatment options and was about to recommend an aggressive combination chemotherapy-irradiation regimen, but she would have none of it. After some discussion, she elected to proceed with weekly fluorouracil injections, even though she was eager to get back home on the range. Over the ensuing four months Marion improved, and the palpable mass regressed until I was no longer able to feel it through the abdominal wall. Every week we swapped stories, she telling me about her life in Montana and me telling her about some of my medical school experiences. A camaraderie somewhat atypical in a physician-patient relationship had evolved.

Marion went back to Montana, and I arranged for her to continue her therapy there, but she did not follow through. About six months later, I received a phone call from the referring physician asking me to see her again. She showed up in the office a few days later for what turned out to be her last consultation with me.

Marion had obvious local recurrence in the abdomen, but without metastatic disease. I decided to offer her radiation therapy, but after hearing about the possible side effects, she elected to go back home to die under the care of her family physician. Two months later, I received a letter from the physician thanking me for my care, telling me that Marion had thought I was "the greatest," and that she had died comfortably with the aid of morphine.

A young physician does not like to lose patients, particularly when they also become friends. I felt at the time that I had let Marion down by not pushing more aggressive therapy on her, so that she might have lived a year or two more.

A month later I was asked to see Wilma, also a 45-year-old woman with stomach cancer. She had long, stringy black hair; a thin, peaked face; and pale complexion, and seemed to cower on the edge of the bed when I approached. A diagnosis of schizophrenia had been recorded in her chart. She did not appear to be a good candidate for radiation therapy. The pathology and operative reports were equally grim: a poorly differentiated adenocarcinoma in the antrum had been resected. Tumor was seen to extend up to resection margins, and 18 of 20 lymph nodes contained metastatic disease.

I had a hard time getting a history. She was distant and scattered during the interview. I decided to offer her radiation treatment as a palliative measure, and after a few

(Odell R Jr: Who's in charge here, anyway? West J Med 1994; 161:429-430)

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formalities, I made my pitch. Something I said concentrated her attention briefly. She became more focused, and then she unexpectedly muttered something under her breath in response to my questions.

"What did you say?" I asked, leaning over the bedside. "I'm sorry, I couldn't hear you."

For the first time, she looked straight into my eyes and spoke in a soft but distant voice. "I'm in God's hands now. You can do whatever you want with me." With that tenuous, informed consent, I scurried out of the room, wishing I had never gotten into this situation.

We started her therapy several weeks later. Throughout the entire series of 35 treatments, Wilma never complained of a single side effect. I asked about the usual and expected nausea and vomiting, anorexia, diarrhea, abdominal pain, or cramping. Despite repeated questioning, Wilma denied having any symptoms. She would quietly slip into the department, occupy a chair as far away from everyone as she could get, submit to her daily dose when called, and then leave as inconspicuously as she came, seemingly unaffected by the onslaught of ionizing radiation she was receiving to her upper abdomen. The staff and I were amazed at her lack of symptoms.

But what has happened subsequently is even more amazing. Incredible as it may seem, Wilma is cured. She has been observed for more than 20 years and has never had a recurrence or a complication related to her therapy. In one of those unexpected happenings, for reasons unknown to the most astute oncology "expert," Wilma remains free of disease. Her schizophrenia is unchanged, waxing and waning as it will. She continues to thank me profusely for "saving her life," but my suspicion is that I had little to do with her favorable clinical outcome.

You see, I was never in charge, even though I thought I was at the time. I have since learned it is the patient interacting with the therapeutic milieu who controls the healing process, and we physicians are privileged witnesses to the miracle of healing as it unfolds. What goes on inside a patient will often determine results more than any intervention we may do.

Physicians understand this fundamental truth because we see it day in and day out in our practices. We need to communicate this kind of information to those nonphysicians responsible for reforming our health care system. Perhaps if we explained to them who is really in charge, they will better appreciate medicine as the art form it is.

Lessons From the Practice

Treachery of the Hysterical Diagnosis

LARRY E. DAVIS, MD, *Albuquerque, New Mexico*

Chief residency is the culmination of physicians' training—when they are finally able to make decisions with authority and confidence. And then patients come along, bringing with them lessons in humility.

Helen was a retired psychiatric nurse who arrived one evening in the emergency department saying that she could not move her legs. She was calm as she explained that the painless paralysis developed while she was watching a news story on Governor George Wallace, who had become paraplegic after being shot in the back. Discovering she could not walk, she somehow was able to go to bed that night and arrived at the emergency department the next day with a neatly packed suitcase. On examination she had normal muscle tone in the legs, but with effort she could barely lift her feet off the bed. All her test results were normal.

Nurses on her former psychiatry ward told me she had always been slightly eccentric. The psychiatry chief resident and I concluded she was hysterical, and we joked about calling her illness "Wallace hysterical paraplegia" or even "the Wallace syndrome." When we announced she could get up, go home, and start psychiatric counseling in the morning, she would not move. An hour passed. I was left with no choice but to call the medical intern and have her admitted to the hospital. Confidently I told the intern my diagnosis and went home.

Early the next morning I awoke with an inexplicable feeling that something about my diagnosis was amiss, and I quickly walked to the hospital. Helen politely wondered why I had awakened her so early as she still felt the same. Now, however, her legs were paralyzed, flaccid, and lacked deep tendon reflexes. My previous confidence turned to anxiety as I called a radiology colleague to do an emergency myelogram.

During a lull in the myelogram, I reviewed her initial laboratory findings. A pit formed in my stomach on finding that her electrocardiogram contained the configuration of an acute myocardial infarction. After the myelogram was completed, we headed for the coronary care unit.

Helen's myocardial infarction resolved, but the associated anterior spinal artery occlusion left her permanently paraplegic. Her calm demeanor remained unchanged, and she left pleased with our care. Yet, I was not pleased and fully realized the treachery of the hysterical diagnosis. Carelessly made, it was—and usually is—wrong. I had been so pleased with my diagnosis and its association with the George Wallace tragedy that I had failed to examine her admission electrocardiogram carefully. In addition, I learned how important it is to listen to patients and to clarify and understand their responses. On more careful questioning, Helen explained how she had crawled from the chair to the bed, how she avoided fluids because she knew she would not be able to get to the bathroom, and how a neighbor helped pack her suitcase and carried her to a waiting taxi. She had previously cared for paraplegics, knew what to expect, and was not scared.

Since then, whenever I encounter a weird or apparently implausible history, I remember Helen and ask careful questions, listen to the answers, and search for a possible "organic" explanation.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Davis LE: Treachery of the hysterical diagnosis. West J Med 1994; 161:431)

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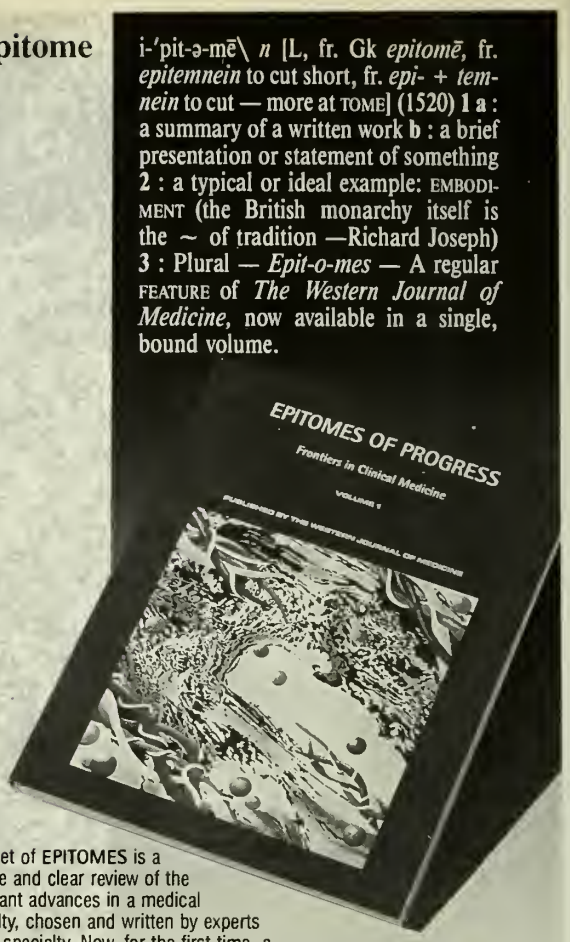

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GENERAL INTERNIST. The department of Medicine at Kern Medical Center has a position for a 8C/8E General Internist to join a growing faculty in a half-time teaching/research endeavor. The Department of Medicine is a UCLA-affiliated Internal Medicine Residency Training Program with a strong emphasis on resident education and patient care. KMC is located in a pleasant central California community. Please send inquiries to Edward L. Arsura, MD, FACP, Chairman, Dept of Medicine, Kern Medical Center, 1830 Flower St, 8akersfield, CA 93305, (805) 326-2200, FAX (805) 326-2950.

DIRECTOR OF AM8ULATORY CARE CENTER. The Department of Medicine at Kern Medical Center has a position for a 8oard Certified General Internist who will take on a newly developed position as Director of our Ambulatory Care Center. This is an exciting position at a new facility requiring well-developed organizational, personal, and educational skills. Kern Medical Center is a UCLA-affiliated Internal Medicine Program with a strong emphasis on resident education and excellence in patient care. KMC is located in a pleasant central California community. Please send inquiries to Edward L. Arsura, MD, FACP, Chairman, Dept of Medicine, Kern Medical Center, 1830 Flower St, 8akersfield, CA 93305, (805) 326-2200, FAX (805) 326-2950.

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Richard Brunader, M.D.
Director, Family Practice Residency Program
Natividad Medical Center
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OREGON. FAMILY PRACTICE clinician teachers needed for Oregon Health Sciences University Department of Family Medicine. We seek clinician teachers for new neighborhood practices. Duties are chiefly patient care plus some resident and student teaching. Obstetrics and hospital care of patients desired. Send CV and three references to L.J. Fagnan, MD, Dept of Family Medicine, OHSU, Mail Code FP Portland, OR 97201-3098. AA/EO Employer.

COME TO THE LAND OF ENCHANTMENT. Sunny New Mexico seeking senior physician for 300-bed state-operated facility for people with developmental disabilities. Seeking individual who is looking for a challenge and personal growth, able to provide primary care to adolescents and adults with developmental disabilities, willing to work on a multidisciplinary team, and willing to provide education to University of New Mexico trainees. Potential for academic appointment. Minimum qualifications: graduation from an accredited medical school, completion of an approved internship and licensure by the New Mexico Board of Medical Examiners. For information contact Javier Aceves, MD at (505) 841-5226.

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CALIFORNIA–SAN LUIS OBISPO AREA. Position available in Urgent Care center on the beautiful central California coast. Competitive compensation, malpractice paid. Prefer physicians with experience or residency training in Emergency Medicine or Family Practice. Send CV to Medical Director, 283 Madonna Rd, Ste B, San Luis Obispo, CA 93405

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(Continued on Page 437)

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CALIFORNIA. MONTEREY BAY. Full- or part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Medicine or Family Practice specialists preferred. Contact Sylvia Amendola, Personnel Director, Doctors on Duty Medical Clinics, 223 Mount Herman Rd, Scotts Valley, CA 95066; (408) 438-9341.

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CALIFORNIA. Ambulatory Care/Family Practice–CEP is a partnership of Ambulatory Care and Emergency Medicine specialists. We currently staff nine free-standing clinics in northern, central, and southern California, and have upcoming openings for physicians specializing in Family Practice. We offer shared ownership, excellent compensation, health, and disability insurance, retirement program, and many other benefits. For more information, send CV or call John Gravette, CEP, 2101 Webster St, Ste 1050, Oakland, CA 94612; (800) 842-2619.

OREGON. Medical Director needed for Oregon Health Sciences University Department of Family Medicine. Duties are to provide patient care and resident and student teaching at the Family Practice patient care clinic. Obstetrics and hospital care of patients desired. Send CV and three references to L.J. Fagnan, MD, Dept of Family Medicine, OHSU, Mail Code FP, Portland OR 97201-3098. AA/EO Employer.

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OREGON–PRACTICE MEDICINE IN THE LUSH, GREEN WILLAMETTE VALLEY. Multi-specialty group seeks BC/BE Internist to join department of eight. Excellent salary plus incentive, outstanding benefits. Salem, the state capital, is 40 miles south of Portland, close to ocean, mountains. Great family community. Contact Yvonne Carscadden, Salem Clinic, 2020 Capitol NE, Salem, OR 97303 or call (503) 399-2470.

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ORTHOPAEDIST–BC/BE, California licensed, needed for San Francisco based multispecialty medical practice. Primarily forensic medical practice (evaluation and expert witness evaluations in workers' compensation, personal injury, etc). Excellent opportunity for experienced clinician looking to emphasize evaluation and consultation practice as opposed to heavy treatment based practice. Full-time and part-time employment available, exceptionally high income potential, full benefits, and 401K. Submit CV and letter stating professional goals and availability to Administrator, 2040 Polk St, Box 337, San Francisco, CA 94109.

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PACIFIC NORTHWEST: WASHINGTON, OREGON, IDAHO. BC/BE physicians needed, Family Practice, Internal Medicine, OB/GYN, Pediatrics, Emergency Medicine Director. Call Eva Page, Page & Associates, Physician Recruiting, (800) 833-3449 or send CV to 1420 NW Gilman Blvd, Ste 2133, Issaquah, WA 98027.

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(Continued on Page 440)

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The **Prescott VA Medical Center** is seeking **BC/BE Internal Medicine physicians,** one with an interest in **Infectious Disease**, as full-time staff physicians to provide primary care. Prescott, the "mile-high" Old West city is conveniently located 98 miles north of Phoenix, the state capital. At an altitude of 5,300 feet, the city is nestled in the mountainous, ponderosa pine area of north central Arizona. Lots of sun in a dry four-season climate, fresh air, and recreation abound. *Money Magazine* rates **Prescott, Arizona** as the **number one city to live in.** Malpractice is covered. Interested and qualified candidates should send CV to:

Bruce Manziello, MD, FACP
Chief of Staff
VA Medical Center
Attn: (11) Prescott, AZ 86313
or call (602) 776-6009

EOE

ACADEMIC FACULTY

OREGON. Faculty needed for **Oregon Health Sciences University,** Department of Family Medicine's Cascades East Family Practice Residency Program Located in Klamath Falls, Oregon.

Seeking faculty to work in concert with the residency director to supervise operation of the Cascades East Family Physician Residency. **Specific duties involve resident teaching; administrative responsibilities for day-to-day operation of clinic; and providing patient care, including obstetric care,** in the office, hospital and off-campus sites under the purview of the Department of Family Medicine. Send CV and three references to:

James F. Clavert Jr, MD
Cascades East FP Residency Program
2800 Daggett
Klamath Falls, OR 97601

AA/EOE

THE CEDARS-SINAI MEDICAL CENTER IS SEEKING AN OB/GYN to lead an academic research unit. This is a full-time faculty appointment in accordance with our affiliation with the UCLA School of Medicine. We seek an individual with an interest in Molecular Oncology and strong clinical skills. The individual must be qualified to participate in active clinical research. Contact James R. Klinenberg, MD, (310) 855-5165 or send CV to: CSMC Room 2211, 8700 Beverly Blvd, Los Angeles, CA 90048. CSMC/UCLA is an affirmative action, equal opportunity employer.

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Northern California multispecialty group has immediate opening for practitioner. Clinical activities involve full range of Internal Medicine. Competitive salary and comprehensive benefit package. CV to: **10978 Donner Pass Rd, Truckee, CA 96161.**

Seattle, Washington, suburb–General Internist. Two Board Certified Internists are seeking a third to start in January 1995. Busy practice. Competitive financial package. Beautiful area. For details, call:
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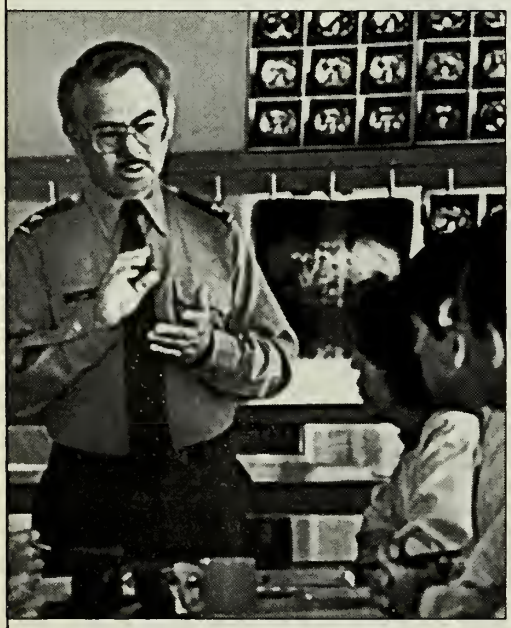

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California Medical Association–PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-7, 1995, Disneyland Hotel, Anaheim.

Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. September 7-10, 1995, The Ritz Carlton Hotel, Aspen.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 5-8, 1995, Hyatt Regency Maui, Hawaii.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 19-21, 1995, Coeur d'Alene Resort.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 5-7, 1995, Village Red Lion, Missoula.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 27-30, 1995, Resort at Squaw Creek, 1995.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. May 12-13, 1995, Albuquerque.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: date to be announced, University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: date and location to be announced.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 8-10, 1995, Jackson Lake Lodge, Moran.

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A CASE STUDY

A 35-year-old man presented with the acute onset of a severe headache. Diagnostic tests revealed an intracranial aneurysm at the junction of the basilar artery and the anterior inferior cerebellar artery, causing sub-arachnoid hemorrhage. Operative approaches for aneurysms in that area are considered difficult and dangerous.

Nevertheless, surgeons at the Center for Skull Base Surgery used a new technique, combining an approach through the temporal bone with newer microsurgical instrumentation.

The otolaryngologist, Dr. Dennis R. Maceri, first drilled out the mastoid, identifying those structures related to hearing that were to be preserved. Dr. Steven L. Giannotta, neurosurgeon, then dissected the aneurysm and put clips on it to obliterate it. Dr. Maceri finished the procedure by closing the brain covering with a watertight fat graft from the patient's lower abdomen.

The patient has made a full recovery and resumed his normal activities of weight lifting, skiing and flying ultra light aircraft.

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However, recent advances in diagnostic imaging and surgical techniques have allowed direct operative management of skull base lesions to become a reality. The advent of magnetic resonance imaging, sophisticated angiography and a better understanding of surgical micro-anatomy in conjunction with improvements in microsurgical instrumentation have enabled previous "inoperable" lesions to now be excised with acceptable risks.

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The USC University Hospital Center for Skull Base Surgery, one of the most comprehensive programs of its kind in the United States, serves as a primary West Coast referral center for intracranial disorders. Members of the interdisciplinary team are committed to maintaining close contact with referring physicians to ensure effective patient management for optimal recovery.

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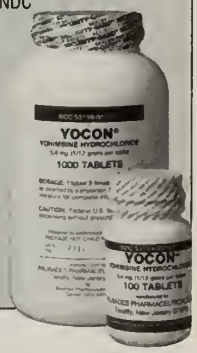

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2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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ABSTRACTS NOVEMBER 1994

(Hjelle B, Jenison S, Mertz G, Koster F, Foucar K: Emergence of hantaviral disease in the southwestern United States. West J Med 1994; 161:467-473)

Hantaviruses are parasites of small mammals, predominantly peridomestic and commensal rodents. They have a worldwide distribution. Hantavirus-related illness occurs in rural areas where humans come into contact with rodents. In most cases human infection is manifested by one of a variety of acute illnesses involving hemorrhagic fever and renal disease. In May 1993, a cluster of patients with an acute pulmonary disease with high mortality was noted in the Four Corners region of the southwestern United States. Serologic and genetic studies indicated that the etiologic agent was a novel hantavirus. The uncertainty engendered by the emergence of a new disease with high mortality forced a rapid response by state and federal agencies and by the University of New Mexico Medical Center, Albuquerque, where most patients from this region were referred. Considerable progress has been made in identifying infected cases on clinical and laboratory grounds and in ensuring that appropriate supportive care is made available to patients as soon as they are suspected of having hantaviral infection. Cases of hantavirus pulmonary syndrome—both new and retrospectively diagnosed—are still being recognized throughout the western United States. Many important questions remain unanswered.

HANTAVIRUS KOREAN HEMORRHAGIC FEVER
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(Hjelle B, Jenison S, Mertz G, Koster F, Foucar K: Emergence of hantaviral disease in the southwestern United States. West J Med 1994; 161:467-473)

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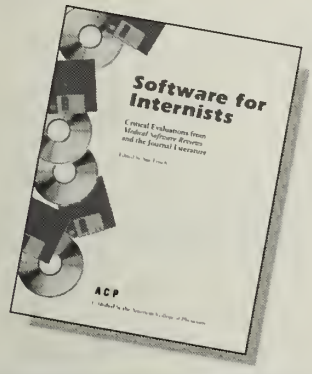

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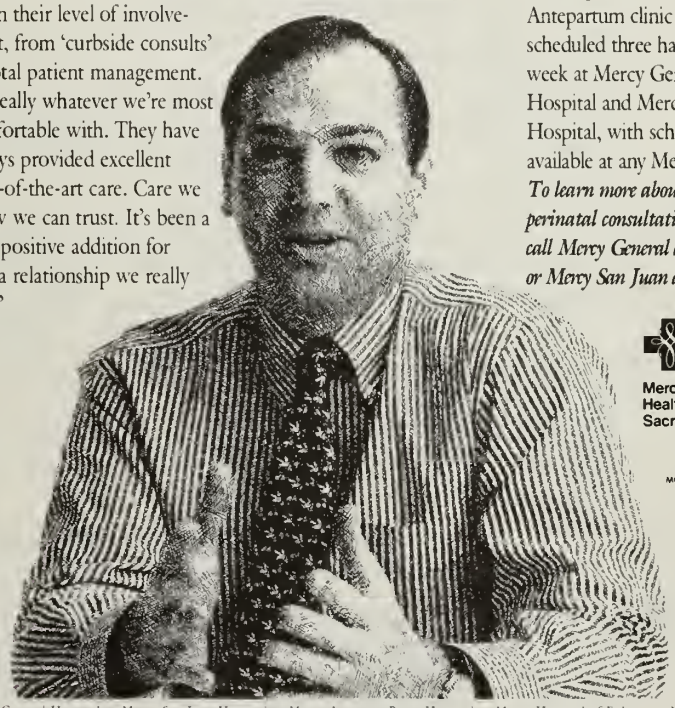

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

December 2-3—**Advanced Operative Laparoscopy for the Gynecologic Oncologist.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri-Sat. Contact: Lynne Mascarella, U of A.

December 2-4—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Hyatt Regency, Scottsdale. Fri-Sun. Contact: Karen DeBont, (800) 421-3756.

December 8-9—**Advanced Cardiac Life Support Provider Course.** Maricopa Medical Center, Phoenix. Thurs-Fri. Contact: (602) 267-5414.

January 12-13—**2nd Annual Current Topics in Critical Care Medicine.** Mayo Clinic-Scottsdale at the Ritz-Carlton Hotel, Phoenix. Thurs-Fri. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 14-15—**5th Annual Current Topics in Anesthesiology.** Mayo Clinic-Scottsdale at the Ritz-Carlton Hotel, Phoenix. Sat-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 20-22—**Electromyography in Clinical Practice.** Mayo Clinic-Scottsdale. Fri-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 25-27—**Clinical Recognition and Management of Heart Disease.** American College of Physicians and Univ of Arizona College of Medicine at University Medical Center, Tucson. Wed-Fri. Contact: (215) 351-2400, ext 2600.

February 6-10—**Psychopharmacology Review Course.** University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Mon-Fri. Contact: Lynne Mascarella, U of A.

February 12-16—**International Congress VIII on Endovascular Interventions: Breaking the Barriers.** American College of Angiology at the Phoenician Resort, Scottsdale. Sun-Thurs. Contact: (602) 266-2200.

February 16-18—**Mayo Interactive Surgical Symposium.** Mayo Clinic-Scottsdale at the Orange Tree Golf and Conference Resort, Scottsdale. Thurs-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 19-22—**Practical Radiology.** University of Arizona College of Medicine at Loews Ventana Canyon Resort, Tucson. Sun-Wed. Contact: Lynne Mascarella, U of A.

February 23-24—**Hepatology Update 1995.** Mayo Clinic-Scottsdale at the Ritz-Carlton, Phoenix. Thurs-Fri. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 24-25—**Mayo Plastic Surgery Symposium.** Mayo Clinic-Scottsdale at the Ritz-Carlton Hotel, Phoenix. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 24-26—**1995 Scientific Assembly—American Academy of Family Practice.** The Pointe Hilton at Tapatio Cliffs, Phoenix. Fri-Sun. Contact: American Academy of Family Practice, Arizona Chapter, (602) 249-2021.

March 5-9—**Radiology in the Desert: Practical Aspects of Radiology and Imaging.** University of Michigan Medical School at Marriott's Camelback Inn Resort, Scottsdale. Sun-Thurs. Contact: Lynne Mascarella, U of A.

March 8-10—**Clinical Reviews 1995.** Mayo Clinic-Scottsdale at the Ritz-Carlton, Phoenix. Wed-Fri. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 11—**Frequently Encountered GYN Problems in Primary Care.** Mayo Clinic-Scottsdale at the Ritz-Carlton, Phoenix. Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 11—**Controversies in Hypertension.** Mayo Clinic-Scottsdale at the Ritz Carlton, Phoenix. Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 30-April 1—**4th Annual Urogynecology and Disorders of the Pelvic Floor.** Mayo Clinic-Scottsdale at The Pointe Hilton Resort at Tapatio Cliffs, Phoenix. Tues-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

April 5-8—**Primary Care Update.** University of Arizona College of Medicine at the Tucson East Hilton. Wed-Sat. Contact: Lynne Mascarella, U of A.

May 7-11—**Fundamental Principles of Pharmacokinetics and Toxicokinetics for the Industrial Scientist.** University of Arizona College of Medicine at the Westward Look Resort, Tucson. Sun-Thurs. Contact: Lynne Mascarella, U of A.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

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ANESTHESIOLOGY

January 4-7—**Anesthesia Update.** UCSD at Hotel del Coronado, San Diego. Mon-Sat. 21 hrs. $350. Contact: UCSD.

February 3-5—**33rd Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: David Steward, MD, Director, PO Box 54700, Los Angeles 90054. (213) 669-2262.

CARDIOLOGY

December 9-11—**12th Annual Advances in Heart Disease.** American College of Cardiology at San Francisco. Fri-Sun. 16.5 hrs. Contact: ACC, 911 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.CME Listing - November 1994

April 28-30—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Sheraton Desert Inn, Las Vegas. Fri-Sun. 11 hrs. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

CRITICAL CARE

March 13-17—**Critical Care Medicine.** USC at Caesars Palace, Las Vegas. Mon-Fri. 33 hrs. $595-$720. Contact: USC.

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CONTINUING MEDICAL EDUCATION

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January 31-February 4—**Critical Care by Design**. Society of Critical Care Medicine at Moscone Center, San Francisco. Tues-Sat. 30.5 hrs. $600. Contact: SCCM, 8101 E Kaiser Blvd, Anaheim 92808-2259. (714) 282-6000.

EMERGENCY MEDICINE

December 4-9—**15th Annual Conference: Current Concepts in Emergency Care.** American College of Emergency Physicians at Maui Intercontinental Resort, Hawaii. Sun-Fri. 20 hrs. Contact: Kailani World Travel, 4192 Meridian Ave, Box 9751, Bellingham, WA 98227. (800) 544-9269 or (206) 671-1800.

December 12-16—**Emergency Medicine Symposium.** UCSD at Basic Science Building. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 16-20—**Emergency Medicine Symposium.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 24-29—**California Trauma Conference.** UCSD at Hyatt Regency, San Diego. Tues-Sun 20 hrs. $395.Contact: UCSD.

March 13-17—**Emergency Medicine Symposium**. UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

EPIDEMIOLOGY/INFECTIOUS DISEASE

January 25-27—**Epidemiology & Prevention of Infectious Disease**. UCSF at Ritz-Carlton, San Francisco. Wed-Fri. 17 hrs. Contact: UCSF.

April 2-4—**5th Annual Meeting of the Society for Healthcare: Epidemiology of America.** UCSD at Town & Country, San Diego. Sun-Tues. 17 hrs. $435. Contact: UCSD.

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(Continued from Page 453)

FAMILY PRACTICE/PRIMARY CARE

December 9-11—**Neurology for the Non-Neurologist.** American College of Emergency Physicians at Desert Inn, Las Vegas, Nevada. Fri-Sun. 12 hrs. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

December 24-29—**Advances in Medicine '94.** American Academy of Family Physicians and Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Lahaina, Maui, Hawaii. Sat-Thurs. 16 hrs. Contact: Joe Harrison, MD, PO Box 10185, Lahaina, HI 96761. (808) 878-6757.

January 20-22—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 2-4—**Neurology for the Non-Neurologists.** UCSD at Doubletree Hotel, San Diego. Thurs-Sat. Contact: UCSD.

February 7-April 25—**Common Problems in Primary Care**. USC at Health Sciences Campus, Los Angeles. Tuesday Evenings. 36 hrs. $475. Contact: USC.

February 14-19—**The Practicing Physician's Approach to the Difficult Headache Patient.** Dannemiller Memorial Educational Foundation at Marriott's Rancho Las Palmas Resort and Country Club, Rancho Mirage. Tues-Sun. Contact: Diamond Headache Clinic, 5252 N Western Ave, Chicago, IL 60625. (312) 907-6226.

February 17-19—**Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 29-31—**Annual Review in Family Medicine.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 16 hrs. $325. Contact: UCSF.

April 10-13—**Primary Care in Paradise: Maui 1995.** Scripps Clinic and Research Foundation at Embassy Suites Resort, Kaanapali Beach, Maui, Hawaii. Mon-Thurs. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs, (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

April 27-30—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at San Diego Princess Resort. Thurs-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, P.O. Box 84296, San Diego 92138. (619) 223-2997.

GERIATRICS

January 17-20—**Intensive Course in Geriatric Medicine**. UCLA at Ritz-Carlton, Marina del Rey. Tues-Fri. 36 hrs. $675. Contact: UCLA.

INTERNAL MEDICINE

December 4—**Complications in Diabetes.** USC at Red Lion Hotel, Glendale. Sun. 5.5 hrs. $45. Contact: USC.

February 1-4—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Hyatt, San Diego. Wed-Sat. 24 hrs. $550. Contact: UCSD.

February 8-14—**Esophageal and Foregut Disorders**. USC at Hyatt Regency Hotel, Kauai, Hawaii. Wed-Tues. 30 hrs. $650. Contact: USC.

February 15-17—**Recent Advances in Neurology**. UCSF at Ritz-Carlton Hotel, San Francisco. Wed-Fri. 15.5 hrs. $365. Contact: UCSF.

February 25—**Sjogren's Syndrome: A Symposium for Patients and Professionals.** USC at Louis B. Mayer Teaching Center, Los Angeles. Sat. 4.5 hrs. $85. Contact: USC.

March 16-18—**Recent Advances in Hematopoietic Stem Cell Transplantation.** UCSD at Hyatt Regency, La Jolla. Thurs-Sat. 16 hrs. $300. Contact: UCSD.

March 17-23—**Internal Medicine 1995: A Comprehensive Review.** Continuing Medical Education Associates at Hotel del Coronado. Fri-Thurs. 54 hrs. $695. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 25-April 1—**Diagnostic and Therapeutic Skills in Internal Medicine.** USC at Hapuna Prince Hotel, Kamuela, Hawaii. Sat-Sat. 29 hrs. $595. Contact: USC.

April 22-23—**Minimal Intervention in Vascular Disease.** Scripps Memorial Hospital and Scripps Clinic and Research Foundation at Hyatt Regency, San Diego. Sat-Sun. Contact: Laurel Steigerwald, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OB/GYN

December 1-3—**Obstetrics and Gynecology Conference.** University of Nebraska Medical Center at Bally's, Las Vegas, Nevada. Thurs-Sat. $275. Contact: UNMC, 600 S 42nd St, Omaha, NE 68198-5651. (800) 642-1095 or (402) 559-4152.

February 9-12—**50th Annual Postgraduate OB/GYN Assembly.** Obstetrical and Gynecological Assembly of Southern California at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OGASC, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

February 18-24—**Perinatal Medicine.** USC at Westin Maui Hotel, Hawaii. Sat-Fri. 30 hrs. $595. Contact: USC.

ONCOLOGY

February 20-23—**Clinical Hematology and Oncology:** 1995. Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 28 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 10-14—**20th Annual Conference: Diagnostic Approaches to Lymphoproliferative Disorders.** Scripps Clinic and Research Foundation at Ritz-Carlton, Maui, Hawaii. Mon-Fri. 26 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OPHTHALMOLOGY

December 8-10—**New and Practical Approaches to Glaucoma Management.** UCSF at Ritz-Carlton Hotel and UCSF, San Francisco. Thurs-Sat. 13.5 hrs. $200-$395. Contact: UCSF.

(Continued on Page 455)

CONTINUING MEDICAL EDUCATION

(Continued from Page 454)

December 9-10—**1st Annual West Coast Cosmetic Eyelid Rejuvenation Symposium**. Medical Education Resources at Beverly Hilton, Beverly Hills. Fri-Sat. 14 hrs. $575. Contact: Angela O'Mara, (714) 760-1522.

January 14—**Primary Care Ophthalmology.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

OTOLARYNGOLOGY

December 4-9, January 8-13—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 55 hrs. $1,100-1,300. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

PATHOLOGY

December 4—**Selected Diagnostic Problems in Surgical Pathology.** California Tumor Tissue Registry at San Diego Marriott. Sun. 8 hrs. Contact: Anne Chism, CTTR, c/o Loma Linda University, 11021 Campus Ave, AH 335, Loma Linda 92354. (909) 824-4788.

December 5-7—**Soft Tissue Pathology: Conceptual and Practical Approaches to Diagnosis.** American Society of Clinical Pathologists at Surf and Sand Hotel, Laguna Beach. Mon-Wed. Contact: ASCP, 2100 W Harrison St, Chicago, IL 60612. (800) 621-4142.

April 8—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundtion. Sat. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

December 1-4—**Society of ENT Advances in Children.** UCD at Radisson Hotel, Sacramento. Thurs-Sun. 10 hrs. Contact: UCD.

(Continued on Page 458)

You are invited to America's favorite vacation city
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of Family Physicians

1995 Scientific Assembly • San Francisco, California
January 27–30

Essential information • Excellent value • 20 CME hours

Program highlights include:

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- topical clinical updates and procedural training for primary care physicians.

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MEMORIAL/UCI CENTER FOR HEALTH EDUCATION

DECEMBER, 1994

7th Annual Obstetrical and Transvaginal Ultrasound Course
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DOUBLETREE HOTEL
ORANGE, CALIFORNIA

Laser Bronchoscopy, Stents, Brachytherapy
December 1-2, 1994
LONG BEACH MEMORIAL MEDICAL CENTER
LONG BEACH, CALIFORNIA

Thoracoscopy for the Pulmonologist
December 3, 1994
LONG BEACH MEMORIAL MEDICAL CENTER
LONG BEACH, CALIFORNIA

JANUARY, 1995

10th Annual Perinatal Symposium
January 11-15, 1995
THE INN AT BEAVER CREEK
BEAVER CREEK, COLORADO

Gynecologic Surgery With Special Emphasis on Endoscopic Surgery
January 15-18, 1995
HYATT REGENCY GRANO CAYMAN
BRITISH WEST INDIES

FEBRUARY, 1995

The 2nd Annual Symposium on the Neurologist and Backpain
February 18-20, 1995
LONG BEACH MEMORIAL MEOICAL CENTER
LONG BEACH, CALIFORNIA

16th Annual Symposium—Current Topics in Obstetrics
February 18-25, 1995
THE GANT CONDOMINIUMS
ASPEN, COLORADO

MARCH, 1995

Gynecologic Oncology for the Primary Care Physician
March 19-24, 1995
THE WESTIN RESORT
MAUI, HAWAII

APRIL, 1995

Advanced Urogynecology and Pelvic Surgery
April 5-9, 1995
MARQUIS HOTEL AND VILLAS
PALM SPRINGS, CALIFORNIA

4th Annual OB/GYN Ultrasound—The State of the Art
April 11-14, 1995
WESTIN RESORT
MAUI, HAWAII

20th Annual Care of the Sick Newborn Symposium
April 26-28, 1995
HYATT REGENCY HOTEL
LONG BEACH, CALIFORNIA

MAY, 1995

6th Annual Philip J. DiSaia Society—OB/GYN Symposium
May 19, 1995
DOUBLETREE HOTEL
ORANGE, CALIFORNIA

JUNE, 1995

UCI Family Practice Refresher Course
June 12-17, 1995
LE MERIDIEN HOTEL
NEWPORT BEACH, CALIFORNIA

JULY, 1995

4th Annual Internal Medicine Board Review Course
July 31-August 4, 1995
LE MERIDIEN HOTEL
NEWPORT BEACH, CALIFORNIA

AUGUST, 1995

13th Annual Controversies in Obstetrics and Gynecology
August 2-5, 1995
HAPUNA BEACH PRINCE HOTEL
MAUNA KEA RESORT
ISLAND OF HAWAII

UNIVERSITY OF CALIFORNIA, IRVINE

CENTER FOR HEALTH EDUCATION

LONG BEACH, CALIFORNIA

For further information contact the Center for Health Education ☎ Offices at (310) 933-3811.

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CME CREDITS VARY PER COURSE.

(Continued from Page 450)

507 **High-Resolution Computed Tomography**
ROBERT S. FISHMAN, MD, and ANN N. LEUNG, MD

508 **Preoperative Staging of Lung Cancer**
JEFFREY SHEA, MD, and GLEN A. LILLINGTON, MD

509 **Primary Pulmonary Hypertension**
NORMAN RIZK, MD

510 **Selective Decontamination of the Gastrointestinal Tract to Decrease the Incidence of Pneumonia and Mortality**
ANTHONY M. COSENTINO, MD

510 **Tropical Lung Disease**
OM P. SHARMA, MD

511 **Evaluating Patients With Chest Pain**
JOHN SWEENEY, MD, and NORA GOLDSCHLAGER, MD

ALERTS, NOTICES, AND CASE REPORTS

513 **Porphyria Cutanea Tarda and Hepatitis C Virus Infection in a Patient With Acute Liver Failure**
ROBERT M. JASMER, MD; MARY S. LARSON, MD; and KATHERINE N. WEILBAECHER, MD

From the Department of Medicine, Stanford University School of Medicine, Stanford, California. Dr Jasmer is now with the Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California, San Francisco, Medical Center.

515 **Pulmonary Tuberculosis, Amenorrhea, and a Pelvic Mass**
JOHN H. WEHNER, MD; KORINA DE BRUYNE, MD; FRANK T. KAGAWA, MD; ANTHONY C. CAMPAGNA, MD; WILLIAM A. JENSEN, MD; CARL M. KIRSCH, MD; and ROGER S. ENG, MD

From the Division of Pulmonary and Critical Care Medicine, Stanford University School of Medicine, Stanford, and the Division of Respiratory and Critical Care Medicine and Departments of Medicine and Radiology, Santa Clara Valley Medical Center, San Jose, California.

COMMENTARY

519 **We Tried It Once—Recollections of an Early Government Health Care Program**
WILLIAM P. LONGMIRE Jr, MD

From the Department of Surgery, Division of General Surgery, University of California, Los Angeles, School of Medicine. Dr Longmire is Professor of Surgery, Emeritus, UCLA, and Distinguished Physician, Emeritus, of the Department of Veterans Affairs.

EDITORIALS

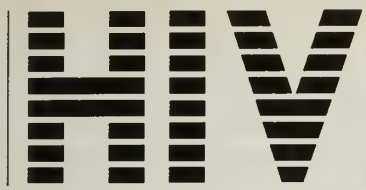
521 **Pharmacologic Management of Benign Prostatic Hyperplasia—Changing Times**
ANTHONY Y. SMITH, MD

From the Department of Surgery, Division of Urology, University of New Mexico School of Medicine, Albuquerque.

523 **How to Capture a Revolution**
DENNIS J. AHNEN, MD

From the University of Colorado Cancer Center, University of Colorado School of Medicine, and Department of Veterans Affairs Medical Center, Denver.

(Continued on Page 460)



7TH NATIONAL AIDS UPDATE CONFERENCE

"Health Care Reform: HIV Today and Tomorrow"

January 31 - February 3, 1995
San Francisco Moscone Convention Center

***Conference Sponsors** (partial list)*

AmFar (American Foundation for AIDS Research)
American Association of Physicians for Human Rights
American Hospital Association
American Medical Association
American Nurses Association
Association of Nurses in AIDS Care
California Academy of Family Physicians
California Association of Hospitals and Health Systems
California Association of Public Hospitals
California Department of Health Services
California Medical Association
California Nurses Association
International Society for AIDS Education
Kaiser Family Foundation
Kaiser Permanente Northern California
Levi Strauss Foundation
National Association of Counties
National Association of People with AIDS
National Association of Social Workers
National Catholic AIDS Network
National Coalition of Hispanic Health and Human Services Organizations (COSSMHO)
National Hospice Organization
National Minority AIDS Council
San Francisco Department of Public Health
San Mateo County AIDS Program
United States Conference of Mayors
University of California EPI Center at San Francisco General Hospital
University of California San Francisco/ AIDS Health Project
Visiting Nurses and Hospice of San Francisco

The primary goal of this Conference is to provide opportunities for discussion among health care service providers, policy makers, funders, educators and program administrators, and persons living with HIV to find the best means to meet the special challenges which the HIV/AIDS epidemic poses.

The Conference is especially relevant for:

- physicians
- policy-makers
- health care providers
- people with HIV/AIDS
- nurses
- pharmacists
- public health agencies
- mental health practitioners
- dentists
- social workers
- program administrators
- government and community leaders
- community-based and HIV/AIDS service organizations, administrators and caregivers
- hospital service and planning managers

Plenary Sessions, nearly 100 Workshops, and nine Intensive Workshops are presented for various levels of attendee knowledge and expertise and bring attention to HIV/AIDS issues in five Conference tracks:

• Policy and Administration • Prevention and Education • Care and Services • Treatment • Cultural Issues

Special events include: Roundtable Talks, Poster Sessions, Film and Theater Festivals, an AIDS in the Arts Display, Resource Center Exhibits, an HIV/AIDS Book Fair, and a display of The NAMES Project AIDS Memorial Quilt.

***Confirmed Speakers To Date** (partial list)*

Inge Corless, PhD, RN, FAAN, Massachusetts General Hospital, Institute of Health Professions, Boston, MA
Elaine Daniels, MD, PhD,Chief, Health Professions, HIV Education Branch, U.S. Public Health Service, Rockville, MD
Donald P. Francis, MD, DSc, Genentech, South San Francisco, CA
Loretta Sweet Gemmott, RN, PhD, FAAN, Assoc. Professor & Dir. of Center for AIDS Research, School of Nursing, Columbia University, NYC
Philip R. Lee, MD, Assistant Secretary for Health, Dept. of Health and Human Services, Washington, DC
Jeff Levi, AIDS Action Council, Washington, DC
Mervyn F. Silverman, MD, MPH, President, AMFAR, Los Angeles, CA
Richard L. Sowell, PhD, RN, FAAN, AID Atlanta, Inc., Atlanta, GA
Paul Volberding, MD, Professor of Medicine, University of California San Francisco. Director, AIDS Program, San Francisco General Hospital, CA

Applications have been submitted for up to 20.5 hours of CME and CEU credit for physicians, nurses and social workers

For general information, to register or exhibit, contact:
KREBS Convention Management Services • 555 DeHaro Street, Suite 200, San Francisco, CA 94107- 2348 • Phone: 415/255-1297 Fax: 415/255-8496

(Continued from Page 455)

December 3—**13th Annual Binational Pediatric Conference.** Children's Hospital San Diego and American Academy of Pediatrics at Mercy Hospital Educational Center, San Diego. Sat. $45. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

December 3-4—**Stabilization and Management of the Critically Ill Child.** UCSF at Mark Hopkins Hotel, San Francisco. Sat-Sun. 9 hrs. $250. Contact: UCSF.

January 21-28—**Pediatric Emergencies.** UCSD at Kona, Hawaii. 21 hrs. $460. Contact: UCSD.

January 23-27—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital San Diego at Town and Country Hotel, San Diego. Mon-Fri. $395. Contact: Children's Hospital, MC 5016, 3020 Children's Way, San Diego 92123. (619) 495-4940.

February 20-22—**Pediatrics Update 1995.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 3-5—**Current Concepts in Pediatric Medicine.** Children's Hospital San Diego at Catamaran Resort Hotel, San Diego. Fri-Sun. $365. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

PSYCHIATRY

January 22-27—**21st Annual Midwinter Program for Psychiatrists.** UCD at Incline Village, Nevada. Sun-Fri. 25 hrs. Contact: UCD.

PULMONARY MEDICINE

February 3-5—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Sheraton Desert Inn, Las Vegas, Nevada. Fri-Sun. 12 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528.

RADIOLOGY

December 8-10—**Magnetic Resonance Angiography in Clinical Practice with CTA Correlation.** UCSF at Ritz-Carlton, Rancho Mirage. Thurs-Sat. 12.5 hrs. $425. Contact: UCSF.

December 11-16—**A Practical Approach to Breast Imaging.** UCSF at Ritz-Carlton Kapalua, Maui, Hawaii. Sun-Fri. 20 hrs. $595. Contact: UCSF.

March 5-9—**Neuro and Musculoskeletal MR.** UCSD at Hotel Del Coronado, San Diego. Sun-Thurs. 30 hrs. $600. Contact: Dawne Ryals, Ryals & Associates, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 5-10—**General Radiology Review.** UCLA at Guest Quarters Suite Hotel, Santa Monica. 40 hrs. $420. Contact: UCLA.

April 16-21—**15th Annual Residents' Radiology Review Course.** UCSD at Hotel Del Coronado, San Diego. Sun-Fri. 41 hrs. $600. Contact: Dawne Ryals, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 21—**Interventional Radiology.** UCSD at Hotel Del Coronado, San Diego. 8 hrs. $135. Contact: Dawne Ryals, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 21-23—**Mammography Update and Review.** UCSD at Hotel Del Coronado, San Diego. Fri-Sun. 16 hrs. $350. Contact: Dawne Ryals, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

SLEEP MEDICINE

January 28—**Sleep Medicine: Practices for the 21st Century.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

SURGERY

December 1-2—**Laparoscopic Colon and Rectal Surgery.** USC at Health Sciences Campus, Los Angeles. Thurs-Fri. #1,800. Contact: USC.

December 8-9—**13th Annual Neurosurgical Nurses' Conference.** UCSF at Hyatt Regency Embarcadero, San Francisco. Thurs-Fri. 13.5 hrs. $325. Contact: UCSF.

January 13-14—**What's New in General Surgery: 17th Annual Postgraduate Course.** UCD at Hyatt Hotel, Sacramento. 15 hrs. Contact: UCD.

January 13-15—**Annual Meeting of the California Association of Neurological Surgeons**: Health Care Reform. California Association of Neurological Surgeons at Four Seasons Hotel, Newport Beach. Fri-Sun. 7 hrs. Laurie Alexander, (916) 971-3524.

February 3-4—**Colon and Rectal Surgery**. USC at Ritz-Carlton Huntington Hotel, Pasadena. Fri-Sat. Contact: USC.

February 6-10—**18th Annual San Diego Postgraduate Assembly in Surgery.** UCSD at Hyatt Islandia, San Diego. Mon-Fri. 26 hrs. $475. Contact: UCSD.

Fehruary 11-12—**Endoscopic Plastic Surgery and Beyond**. UCSD at BSB and Thornton Hospital, La Jolla. Sat-Sun. 13 hrs. $1250. Contact: UCSD

April 20-22—**Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton Hotel, Nob Hill, San Francisco. Thurs-Sat. Contact: UCSF.

April 29-30—**Endoscopic Plastic Surgery and Beyond.** UCSD at UCSD BSB and Thornton Hospital, La Jolla. Sat-Sun. 13 hrs. $1250. Contact: UCSD.

GENERAL/MULTIDISCIPLINARY

February 13-17—**Physician Heal Thyself.** UCSD at Sheraton Harbor Island, San Diego. Mon-Fri. Contact: UCSD.

February 16-19—**2nd International Congress on Vitamins and Biofactors in Life Science.** Thurs-Sun. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 18-21—**Molecular Approaches to Laboratory Diagnosis.** UCSF at Ritz-Carlton, San Francisco. Sat-Tues. Contact: UCSF.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

January 28-February 2—**24th Annual Mid-Winter Conference of Colorado Ophthalmological Society.** Sheraton Steamboat, Steamboat Springs. Sun-Thurs. Contact: David R. Scott, (800) 394-4968.

February 20-24—**19th Midwinter Symposium on Practice Surgical Challenges in Otolaryngology.** University of Illinois College of Medicine at Snowmass. Mon-Fri. Contact: Jane Whitener, (312) 996-5751.

February 26-March 3—**Ninth Annual Cardiology for the Clinician Conference: Practical Guidelines for Merging Advances in Cardiology and Bedside Medicine.** University of Illinois College of Medicine at Snowmass. Mon-Fri. Contact: Sue Talbert, (312) 996-4631.

March 5-10—15th **Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Medical Center, (402) 559-4152 or (800) 642-1095; FAX (402) 559-5915.

March 12-15—**5th International Conference on Pulmonary Rehabilitation and Home Ventilation**. National Jewish Center for Immunology and Respiratory Medicine and American Association for Respiratory Care at Hyatt Regency, Denver. Sun-Wed. Contact: Adele Gelfand, (303) 398-1359 or 270-2171.

July 28-August 1—**80th Annual Summer Conference**. Colorado Ophthalmological Society at Sheraton Steamboat Resort, Steamboat Springs. Fri-Tues. Contact: David R. Scott, (800) 394-4968; FAX (303) 438-9602.

(Continued on Page 459)

CONTINUING MEDICAL EDUCATION

(Continued from Page 458)

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 270-6761.

IDAHO

February 17-19—**Ada County Medical Society—36th Annual Medical Winter Clinics—From Trauma to Rehab.** Shore Lodge Inn, McCall. Fri-Sun. 9 hrs. $125, members; $175, nonmembers. Contact: Ada County Medical Society, Box 2668, Boise 83701; Judy Barningham, (208) 336-2930 or Marie Chester, (208) 386-2135.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance.

(Continued on Page 462)

3RD AMBULATORY HEALTH CARE ACCREDITATION CONFERENCE

The California Medical Association's Ambulatory Care Review Committee and the Accreditation Association for Ambulatory Health Care, Inc. present the third Ambulatory Health Care Accreditation Conference on December 2, 1994, at Le Meridien Newport Beach Hotel.

All aspects of the CMA-AAAHC Ambulatory Review Program will be addressed including:

- Review of the 1994–95 Standards and Criteria
- Survey preparation, details of the survey process and on-site procedures.
- Implementation and application of quality management in the ambulatory setting.
- Workshop on developing appropriate quality management studies.

Approved for three hours of Category I credit.

For further info & registration, please contact: Anne Ahrens, California Medical Association, 415/882-5174.

University of Colorado's

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For further information contact the Office of Continuing Medical Education at (800) 882-9153 or (303) 372-9050.

Eligible for Category I AMA credit hours.

1994-1995 FALL/WINTER/SPRING SERIES HIGHLIGHTS

NOVEMBER 1994

1. Family Practice Review
   November 7-11, 1994 Denver, CO

DECEMBER 1994

2. 3rd Annual Update in Infectious Disease: Bugs and Drugs
   December 9-10, 1994 Denver, CO

JANUARY 1995

3. Anxiety and Depression
   January 20-21, 1995 Denver, CO

FEBRUARY 1995

4. 21st Annual OB/GYN Conference
   February 20-24, 1995 Vail, CO
5. Team Approach to Pediatric Cardiac Disease
   February 26-March 1, 1995 Vail, CO
6. Horizons in Surgery
   February 25-March 4, 1995 Breckenridge, CO

MARCH 1995

7. CRASH '95: Colorado Review of Anesthesia
   March 3-10, 1995 Vail, CO
8. Neurosurgery in the Rockies
   March 5-9, 1995 Vail, CO
9. Reconstructive Surgery of the Hip and Knee
   March 11-18, 1995 Telluride, CO
10. Colorado Conference on Patient-Centered Family Practice
    March 12-15, 1995 Denver, CO
11. The Fetus and Newborn
    March 12-15, 1995 Aspen, CO
12. Controversies in Transplantation
    March 30-April 4, 1995 Breckenridge, CO

APRIL 1995

13. The Female Athlete: Enhancing Health & Fitness
    April 7, 1995 Denver, CO

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530 'He Who Saves a Life Saves a Universe'
VICTOR S. SLOAN, MD
At the time this lesson was written, Dr Sloan was a fellow in rheumatology at the University of California, San Francisco, School of Medicine. He is currently a fellow in rheumatology at the Robert Wood Johnson Medical School, New Brunswick, New Jersey.

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★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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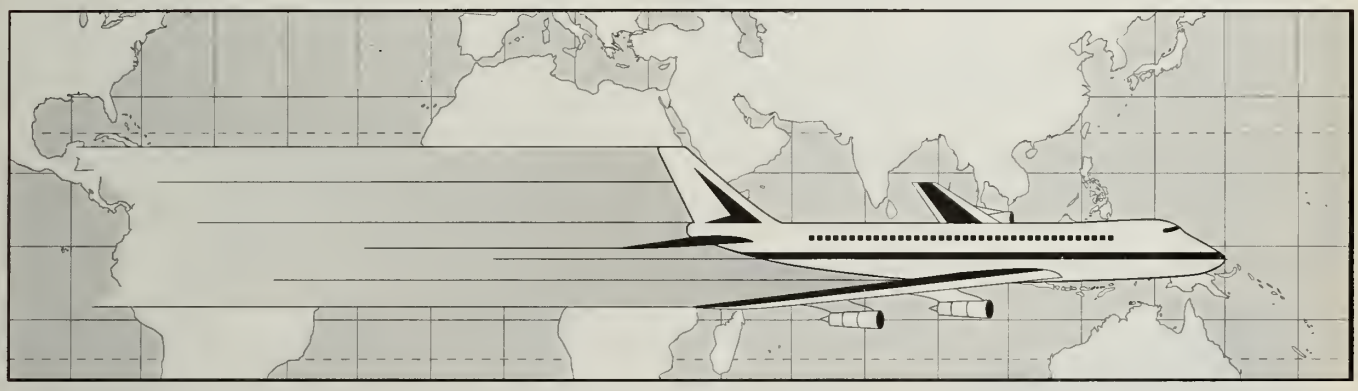

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(Continued from Page 459)

For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

December 1-2—**Annual Meeting—American College of Physicians, New Mexico Chapter/New Mexico Society of Internal Medicine.** Hilton, Albuquerque. Thurs-Fri. Contact: Carol Case, UNM SOM.

April 22—**New Mexico Society of Anesthesiologists—Annual Meeting.** Hilton Hotel of Santa Fe. Sat. Contact: Lynette Hanks, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237 or (800) 748-1596.

July 3-7—**Santa Fe Breast Imaging.** Lovelace Medical Center, Albuquerque, at Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925.

July 7-9—**Health Care Revolution: Where Do We Go From Here?** Lovelace Medical Center, Albuquerque, at Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 3-6—**Sport Medicine and Imaging.** Lovelace Medical Center, Albuquerque, at Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 7-11—**Imaging 1995.** Lovelace Medical Center, Albuquerque, at Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

December 2—**AIDS and Related Diseases.** University of Utah School of Medicine. Fri. Contact: UUSM.

December 3-8—**Intensive MR Imaging and Neuroradiology.** University of Utah School of Medicine at the Marriott Hotel, Salt Lake City. Sat-Thurs. 45 hrs; $1,200. Contact: UUSM.

January 17-22—**Advances in Craniofacial/Oculoplastic and Facial Aesthetic Surgery.** University of Utah School of Medicine at the Cliff Lodge at Snowbird. Tues-Sun. 24 hrs. $525. Contact: UUSM.

January 23-27—**Workshops in Advances MR Imaging, Head and Neck Imaging, and Neuroradiology.** University of Utah School of Medicine. Mon-Fri. Contact: UUSM.

February 6-10—**Surgical Pathology.** University of Utah School of Medicine at the Yarrow Hotel, Park City. Mon-Fri. 20 hrs. $550. Contact: UUSM.

February 20-24—**Workshops in Advanced MR Imaging, Head and Neck Imaging, and Neuroradiology.** University of Utah School of Medicine. Mon-Fri. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

December 2—**Pediatric Update.** Seattle. Fri. Contact: Children's, (206) 526-2501.

December 7-10—**American College of Physicians.** Seattle. Wed-Sat. Contact: U/W.

(Continued on Page 463)

CONTINUING MEDICAL EDUCATION

(Continued from Page 462)

December 8-10—**10th Annual Infectious Disease Conference.** Seattle. Thurs-Sat. Contact: Pacific Northwest Medical Education Institute, (206) 261-2160.

January 26—**Cancer Care Symposium.** Seattle. Thurs. Contact: Providence, (206) 320-2552..

March 2—**Emergency Response in the Workplace: An Occupational Health Nursing Update.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

April 13—**Advances in Occupational and Environmental Medicine.** Seattle. Thurs.Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762. ◆

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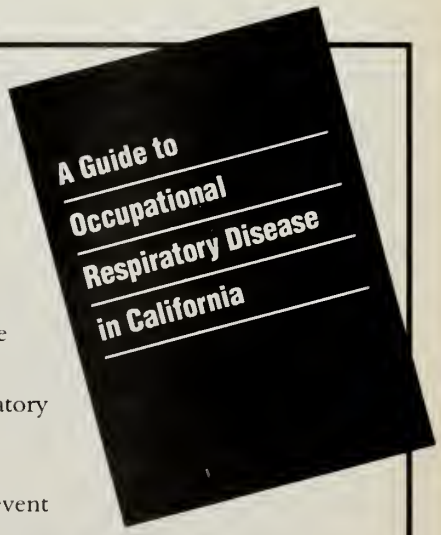

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In Memoriam

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Auerhan, Harold S., Fortuna. Died Aug 3, 1994, aged 75. Graduate of Cornell University Medical College, New York. Licensed in California in 1955. Dr Auerhan was a member of the Humboldt-Del Norte Medical Society.

Dickinson, Philip H., San Diego. Died Aug 1994, aged 71. Graduate of University of Rochester, 1948. Licensed in California in 1955. Dr Dickinson was a member of the San Diego County Medical Society.

Galliher, James E., Brea. Died Aug 14, 1994. Graduate of University of California College of Medicine, Irvine, 1962. Licensed in California in 1975. Dr Galliher was a member of the Orange County Medical Association.

Gruter, Joachim H., Santa Clara. Died Apr 29, 1994, aged 81. Graduate of University of Heidelberg, 1939. Licensed in California in 1968. Dr Gruter was a member of the Santa Clara County Medical Association.

John W. Henrickson, San Diego. Died Aug 1994, age 78. Graduate of Tulane University School of Medicine, New Orleans, 1939. Licensed in California in 1946. Dr Henrickson was a member of the San Diego County Medical Society.

Higgins, George A., Jr, Santa Barbara. Died Sep 3, 1994, aged 77. Graduate of Harvard Medical School, Boston, 1942. Licensed in California in 1983. Dr Higgins was a member of the Santa Barbara County Medical Society.

Hoxie, Derrick A., Alameda. Died Jul 14, 1994, aged 93. Graduate of University of Nebraska College of Medicine, Omaha, 1924. Licensed in California in 1924. Dr Hoxie was a member of the Alameda-Contra Costa Medical Association.

Johnson, Cecilia L., Berkeley. Died Mar 27, 1994, aged 75. Graduate of University of California, San Francisco, 1943. Licensed in California in 1944. Dr Johnson was a member of the Alameda-Contra Costa Medical Association.

Kaufman, Herschel J., Santa Barbara. Died Jun 22, 1994, aged 82. Graduate of University of Minnesota Medical School, Minneapolis, 1935. Licensed in California in 1965. Dr Kaufman was a member of the Santa Barbara County Medical Society.

Peelle, E. Dalton, Newport Beach. Died Jul 29, 1994, aged 87. Graduate of University of Cincinnati College of Medicine, Ohio. Licensed in California in 1951. Dr Peelle was a member of the Orange County Medical Association.

Rice, John L., Sacramento. Died Mar 15, 1994, aged 68. Graduate of University of California, Irvine, 1962. Licensed in California in 1975. Dr Rice was a member of the Sacramento-El Dorado Medical Society.

Shannon, Charles R. Mission Viejo. Died Apr 25, 1994, aged 73. Graduate of Stanford University School of Medicine, 1952. Licensed in California in 1952. Dr Shannon was a member of the Sacramento-El Dorado Medical Society.

Soss, Siedell L., Walnut Creek. Died Aug 26, 1994, aged 65. Graduate of University of Washington School of Medicine, Seattle, 1955. Licensed in California in 1956. Dr Soss was a member of the Alameda-Contra Costa Medical Association.

Denver Medical Society

Leidholt, John Danos. Died Sep 9, 1994, aged 72. Graduate of University of Rochester, Rochester, New York, 1946. Licensed in Colorado in 1956.

Mosko, Joel. Died Aug 31, 1994, aged 82. Graduate of Faculty of Medicine University of Paris, France, 1940. Licensed in Colorado in 1946.

Perreten, Frank Arnold. Died Jul 25, 1994, aged 67. Graduate of University of Pennsylvania, Philadelphia, 1952. Licensed in Colorado in 1953.

New Mexico Medical Society

Redman, Jack C., Albuquerque. Died Sep 12, 1994, aged 70. Graduate of University of Colorado, Denver, 1950. Licensed in New Mexico in 1951. Dr Redman was a member of the Greater Albuquerque Medical Association.

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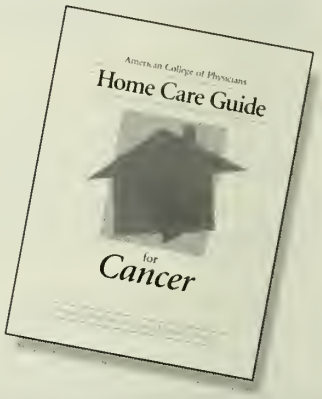

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2. Location of the headquarters or general business office of the publisher: 221 Main Street, 3rd Floor, San Francisco, California 94105.

3. Publisher: California Medical Association, 221 Main Street, 2nd Floor, San Francisco; Editor, Linda Hawes Clever, MD, 221 Main Street, 3rd Floor, San Francisco, California 94105; Managing Editor, Diana McAninch, 221 Main Street, 3rd Floor, San Francisco, California 94105.

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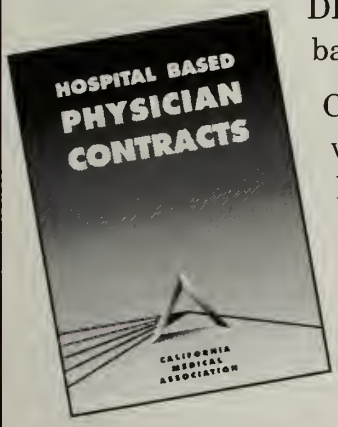

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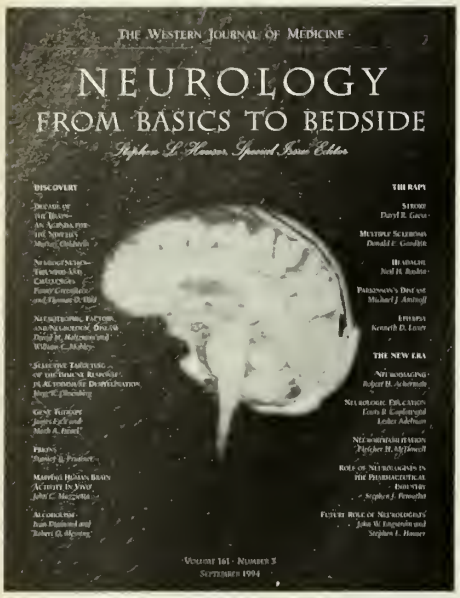

Stephen Hauser, MD
Special Issue Editor, 1994

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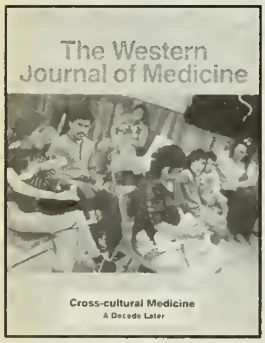

Judith Barker, PhD
Special Issue Editor, 1992

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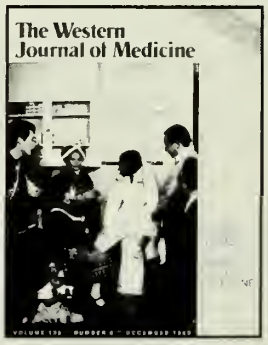

M. Margaret Clark, PhD
Special Issue Editor, 1983

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Emergence of Hantaviral Disease in the Southwestern United States

BRIAN HJELLE, MD; STEVEN JENISON, MD; GREGORY MERTZ, MD;
FREDERICK KOSTER, MD; and KATHRYN FOUCAR, MD, *Albuquerque, New Mexico*

Presented as the Distinguished Lecture at the annual meeting of the Western Association of Physicians, Carmel, California, February 1994.

Hantaviruses are parasites of small mammals, predominantly peridomestic and commensal rodents. They have a worldwide distribution. Hantavirus-related illness occurs in rural areas where humans come into contact with rodents. In most cases human infection is manifested by one of a variety of acute illnesses involving hemorrhagic fever and renal disease. In May 1993, a cluster of patients with an acute pulmonary disease with high mortality was noted in the Four Corners region of the southwestern United States. Serologic and genetic studies indicated that the etiologic agent was a novel hantavirus. The uncertainty engendered by the emergence of a new disease with high mortality forced a rapid response by state and federal agencies and by the University of New Mexico Medical Center, Albuquerque, where most patients from this region were referred. Considerable progress has been made in identifying infected cases on clinical and laboratory grounds and in ensuring that appropriate supportive care is made available to patients as soon as they are suspected of having hantaviral infection. Cases of hantavirus pulmonary syndrome—both new and retrospectively diagnosed—are still being recognized throughout the western United States. Many important questions remain unanswered.

(Hjelle B, Jenison S, Mertz G, Koster F, Foucar K: Emergence of hantaviral disease in the southwestern United States. West J Med 1994; 161:467-473)

In 1951 American troops stationed in Korea were stricken by an unfamiliar and frightening illness. Korean hemorrhagic fever, as it came to be known, was characterized by a prodrome for as long as five days of fever, chills, and myalgia. The prodrome was followed by hemorrhagic manifestations such as gastrointestinal bleeding, subconjunctival hemorrhage, and petechiae, as well as acute renal failure, shock, and pulmonary edema. Laboratory abnormalities included leukocytosis, thrombocytopenia, and hemoconcentration. About 10% of patients died of shock, pulmonary edema, or hemorrhagic complications. Epidemiologic considerations suggested that the disease was a zoonosis.[1,2]

Despite efforts by many virologists, it was not until 1976 that investigators succeeded in isolating the agent. The important breakthrough came after investigators succeeded in detecting viral antigens in the tissues of a suspected rodent host—the striped field mouse, *Apodemus agrarius*—by using serum specimens of patients with Korean hemorrhagic fever as antibody probes. The tissues of the rodent host proved to be a fertile source of Hantaan virus, facilitating its isolation.[3]

Since that time, at least five other relatives of Hantaan virus have been well characterized. Seoul virus, which infects the commensal rat, *Rattus norvegicus*, occurs in port cities throughout the world (Figure 1). This virus causes a syndrome similar to Korean hemorrhagic fever, but generally less severe than that caused by Hantaan virus.[1,4] (The term "hemorrhagic fever with renal syndrome" is now used to encompass the various syndromes caused by Hantaan, Seoul, and Puumala viruses.) Puumala virus causes a relatively mild form of hemorrhagic fever with renal syndrome.[5,6] Prospect Hill virus is the first hantavirus known to occur in a New World rodent species. It has been identified only in the rodent species *Microtus pennsylvanicus* and is not known with certainty to infect humans.[7]

Hantaviral Pulmonary Syndrome

In May 1993 a cluster of patients was identified in western New Mexico and eastern Arizona with a previously undescribed syndrome of pulmonary edema, fever, neutrophilia, and thrombocytopenia.[8-13] Table 1 summarizes the clinical and laboratory abnormalities that have

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control and Prevention
cDNA = complementary DNA
FCV = Four Corners virus
Ig = immunoglobulin
RT-PCR = reverse transcription=polymerase chain reaction

emerged as the hallmarks of the newly identified illness. Patients with the illness were shown by investigators at the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, to have serum immunoglobulin (Ig) M and IgG antibodies that cross-reacted with the Puumala, Prospect Hill, and Seoul hantaviruses. They were able to amplify a small piece of DNA complementary to the RNA of a new hantavirus.[9,11,13] The newly identified hantavirus is commonly known as the Four Corners* virus (FCV), but is also known as Sin Nombre virus or Convict Creek virus. Four Corners virus was found to be most closely related to the Puumala and Prospect Hill viruses based on nucleotide sequence analysis.[13-15] The illness caused by FCV is now known as hantavirus pulmonary syndrome.[16] The host for FCV was shown to be the ubiquitous deer mouse, *Peromyscus maniculatus*.[9,10,13,15] Deer mice trapped in and about the houses of case-patients showed an FCV seroprevalence of about 30%.

The hantavirus pulmonary syndrome is widespread in the United States and is associated with a high mortality. After the identification of the first 5 cases in New Mexico and Arizona, more than 70 cases of the syndrome have been identified in 17 states (Figure 2), dating as far back as 1975.[17] The mortality has been approximately 60%. The wide range of the deer mouse, which spans nearly all of the continental United States (excluding the southeastern states) and much of Canada and Mexico, would suggest that cases will occur in other states as well. Nearly all patients with the hantavirus pulmonary syndrome are from rural areas. In the urban United States, deer mice are uncommon, and the predominant small rodents are the house mouse *Mus musculus* and *Rattus* species. Exposure to possible hosts of FCV in urban dwellers is rare.

Proven or suspected cases of the syndrome have occurred in sites outside of the range of the deer mouse.[11,18] In a case from Louisiana, viral complementary DNA (cDNA) amplified from the tissues of a patient had a genetic sequence that was thought to diverge substantially from that of FCV.[11] The rodent host for that virus has not yet been identified. Viral cDNA from a patient from Florida with possible hantavirus pulmonary syndrome was not amplified. Trapping at the presumed site of infection revealed an enzootic of another, previously unknown, hantavirus, however.[18] The host for the newly identified virus is the cotton rat, *Sigmodon hispidus*.

The hantavirus pulmonary syndrome is a distinctive syndrome. Early manifestations include myalgias, chills, and fever, findings that are similar to those of a variety of more common and less lethal upper respiratory tract illnesses. Some features that are commonly seen with other upper respiratory tract infections, such as pharyngitis and rhinorrhea, are rare in this syndrome, however. Following the initial nonspecific findings, respiratory symptoms, beginning with nonproductive cough and progressing to severe dyspnea, develop in patients with hantaviral infection. Interstitial pulmonary infiltrates and, in many patients, pleural effusion are apparent on radiographic examination. At this point of infection, a profound capillary leak syndrome occurs involving the pulmonary endothelium. The alveolar spaces fill with a highly proteinaceous fluid. If a patient survives the period of acute pulmonary disease and hemodynamic instability, complete recovery occurs within a few days.[16,19]

Certain laboratory abnormalities reflect the abrupt fluid derangements that occur at this point in the illness.[16,19] Hemoconcentration and hypoproteinemia are common. Furthermore, the lactate dehydrogenase level becomes elevated, as does the neutrophil count. A leftward shift is evident, often featuring circulating myelocytes and metamyelocytes. Thrombocytopenia—$< 150 \times 10^9$ per liter (150,000 per mm^3)—is nearly universal, although some patients do not have this sign until after the development of pulmonary disease. Most patients at the University of New Mexico Hospital reached a nadir of 40 to 100 platelets $\times 10^9$ per liter (40,000 to 100,000 per mm^3) (K. F. and F. K., unpublished data, November 1993).

It is common for these patients to be seen in primary care clinics more than once before their condition is recognized as the hantavirus pulmonary syndrome. This pattern continued even in the areas of highest incidence in the Four Corners, well after the syndrome was recognized and described. Because patients initially have nonspecific symptoms, several algorithms are being evaluated in an effort to determine which patients are in the FCV prodromal period and which have other febrile illnesses. Evaluations that show the greatest promise at distinguishing early hantavirus pulmonary syndrome from other illnesses include examining the peripheral blood for thrombocytopenia and the presence of immunoblasts and measuring oxygen saturation.

Dyspnea follows within one to five days after the prodrome starts. Its severity is highly variable. Some patients can be treated without ventilatory assistance, but others die despite admission to an intensive care unit, the use of ventilatory support, pressors, and antiviral therapy.

Hemodynamic Abnormalities

The University of New Mexico Hospital's medical intensive care unit staff was able to monitor the evolution of illness closely for several patients with this illness.[19] Ventricular arrhythmias, hypotension, oliguria, high serum lactate levels, and a pronounced decrease in cardiac output occurred commonly in severe cases, despite adequate oxygenation. Hantavirus pulmonary syndrome could be distinguished hemodynamically from septicemic shock by the high systemic vascular resistance and decreased

*"The Four Corners" refers to the locality in the Southwest that is the only place in the United States where four states—Colorado, New Mexico, Arizona, and Utah—come together.

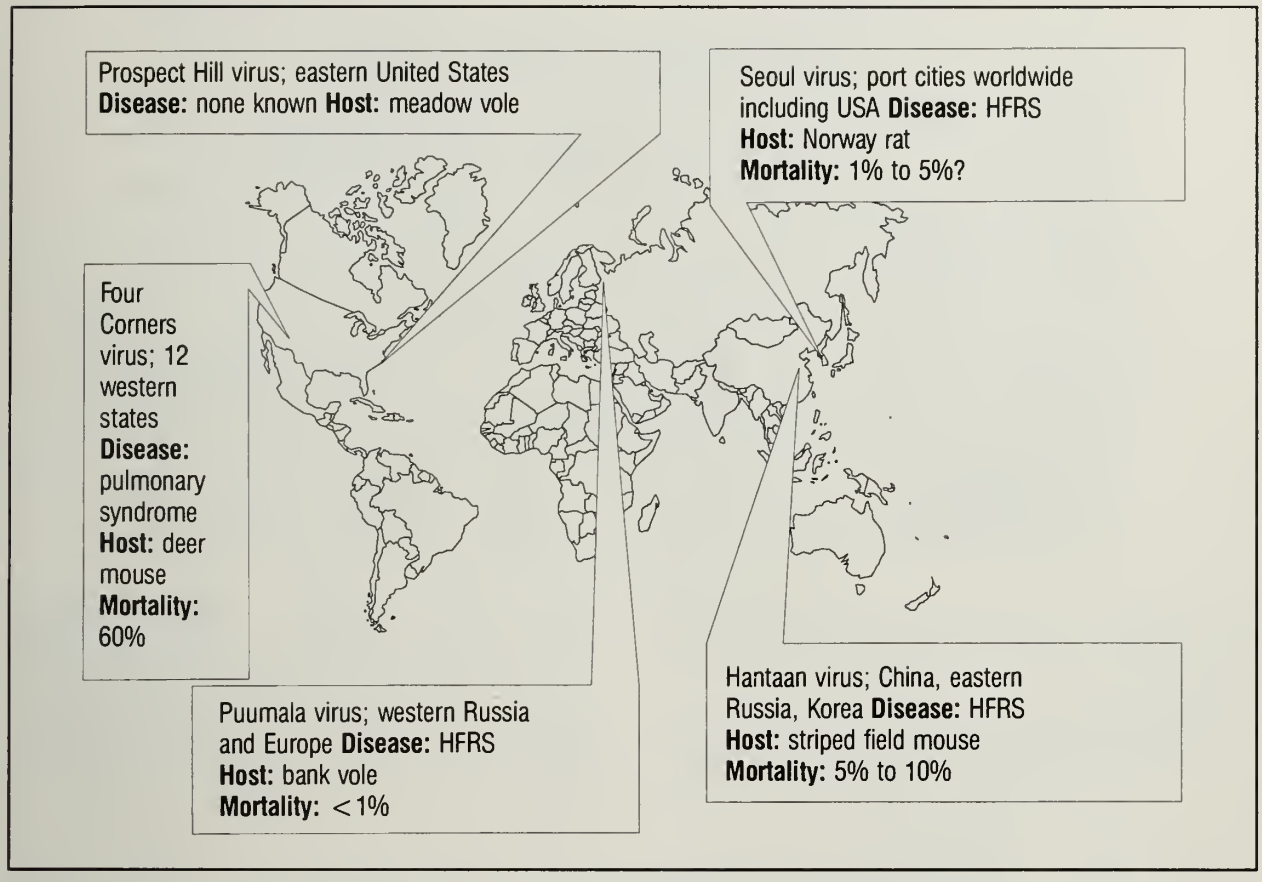

Figure 1.—The map shows the worldwide distribution of hantaviruses. Only viruses that are well characterized and clearly distinguished from others are shown. HFRS = hemorrhagic fever with renal syndrome

cardiac index. Mild hepatitis was nearly universal. Prolonged coagulation times were common, but unlike with hemorrhagic fever with renal syndrome, hemorrhage was not observed in our patients.

Diagnostic Approaches

A means of rapid diagnosis was considered to be an essential part of the response to the new outbreak.[20] The cross-reactivity between FCV and the previously known hantaviruses seemed unlikely to be the basis of a test of sufficient sensitivity and specificity.[21-24] Usually the development of diagnostic capabilities for a newly identified virus follows its propagation in culture. The cultured virus then serves as a source of antigens for diagnostic assays.[23,24] Hantaviruses will grow in cultured cells, but several months are usually required before the virus becomes adapted to culture.

Recent experience with unculturable pathogens such as hepatitis C virus suggested that there was no need to wait for FCV to be grown in culture before a diagnostic method could be developed.[25] In the early weeks of the outbreak, a reverse transcription-polymerase chain reaction (RT-PCR) procedure similar to that used by the CDC in its initial identification of hantaviral RNA in the tissues of patients with the hantavirus pulmonary syndrome was used in a collaboration between investigators at the University of New Mexico School of Medicine and the CDC. Patients in the acute phase of the disease had circulating FCV RNA in their peripheral blood mononuclear cell compartment.[26] The RT-PCR procedure proved to be a helpful diagnostic aid in the initial weeks of the outbreak, but did not represent a practical long-term solution to the problem. A reliable test for FCV antibodies was also needed. Of patients with unexplained respiratory disease, those without the hantaviral syndrome outnumbered those with it by at least 3 to 1, even in the Four Corners area.

Viral proteins or portions of viral proteins can be produced in *Escherichia coli* or other hosts and used as a substrate for detecting antibodies.[25] Because the antigenic domains of viral proteins may lie anywhere within the protein sequence, we chose to molecularly clone the entirety of the FCV nucleocapsid protein gene, as well as the genes for the envelope glycoproteins G1 and G2. We then induced the expression of the corresponding viral proteins in *E coli* and used the proteins in Western immunoblot assays (Figure 3). We soon learned that there were at least two antigenic domains within the viral nucleocapsid and one within the G1 protein.[21,22] All infected patients had brisk and intense reactivity to the nucleocapsid protein, and all reacted with the G1 protein as

TABLE 1.—*Clinical, Epidemiologic, and Laboratory Characteristics That Distinguish Hantavirus Pulmonary Syndrome (HPS) From Other Illnesses*

Characteristic	*Common in HPS*	*Uncamman or Rare in HPS*
Demographic	Rural, indigent, known rodent exposure	Urban, middle class
Age, yr	12-64	(None < 12)
Immunocompromised	No	Yes
Prodrome	Fever, chills, myalgias, cough, abdominal pain, nausea	Rhinorrhea, pharyngitis, otitis
Laboratory test results	Elevated LDH, atypical lymphocytes, polycythemia*, neutrophilia with left shift,* thrombocytopenia	Absolute lymphocytosis
Hospital course	Abrupt recovery or death	Prolonged ventilatory support
Lung disease	Interstitial infiltrates, pleural effusion, O_2 saturation <90%	Purulent sputum, lobar disease
Renal disease	Proteinuria absent or mild	Acute renal failure, massive proteinuria

LDH = lactate dehydrogenase

*More common in severe cases.

well. Thus, a recombinant Western blot assay was defined as positive if IgG or IgM reactivity, or both, could be demonstrated against both the viral nucleocapsid and G1 proteins.[21,22]

We found that the antigenic domain within G1—but not the predominant antigenic domain of the nucleocapsid—was highly variable among hantaviruses. Patients with FCV infection produced antibodies that cross-reacted strongly with the nucleocapsid proteins of the Puumala and Prospect Hill hantaviruses, but FCV G1 antibodies did not recognize the G1 proteins of the other hantaviruses.[21,22] We could not only determine whether

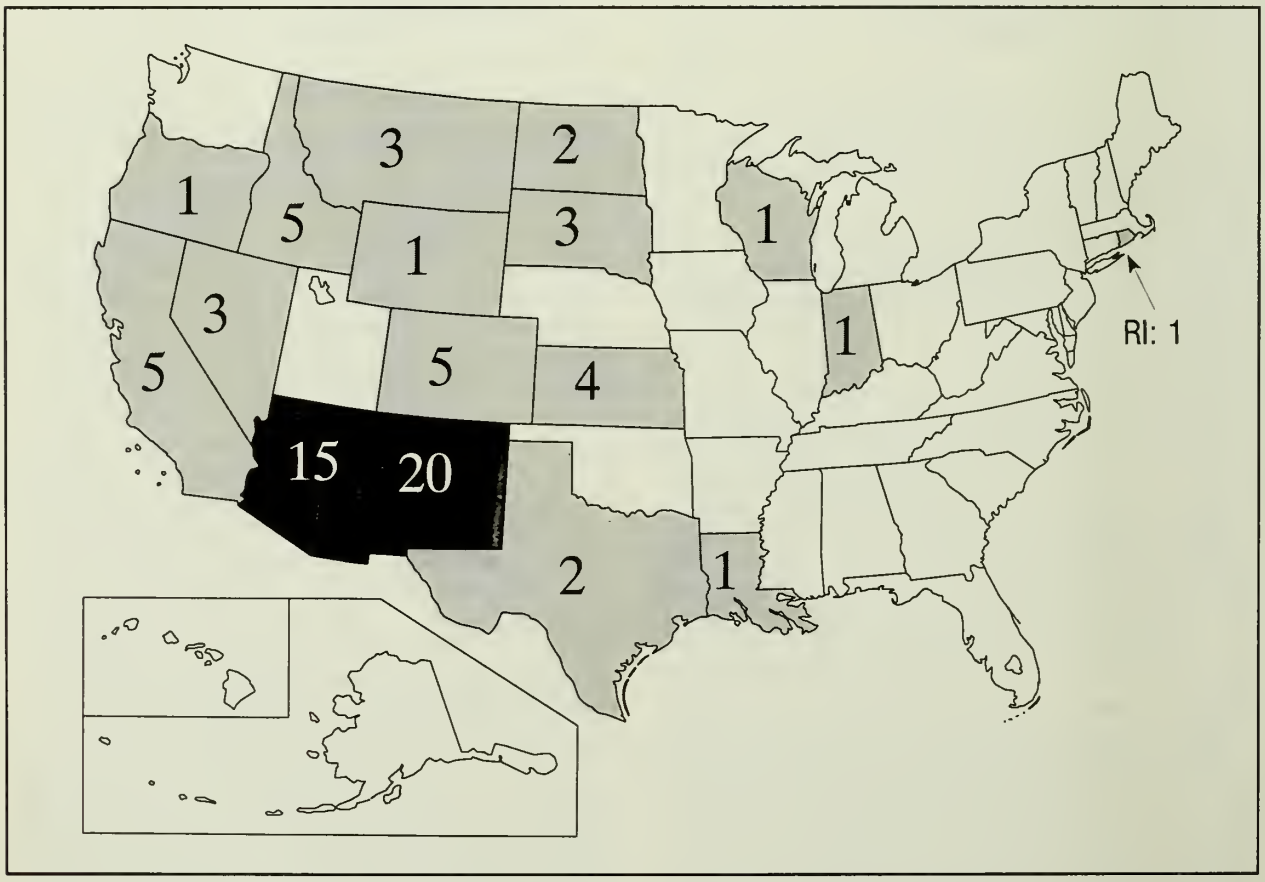

Figure 2.—The caseload of the hantavirus pulmonary syndrome is shown as of early May 1994. States with 1 to 5 cases are light gray, whereas states with more than 10 cases are indicated in black. No cases have thus far been reported outside the United States. RI = Rhode Island

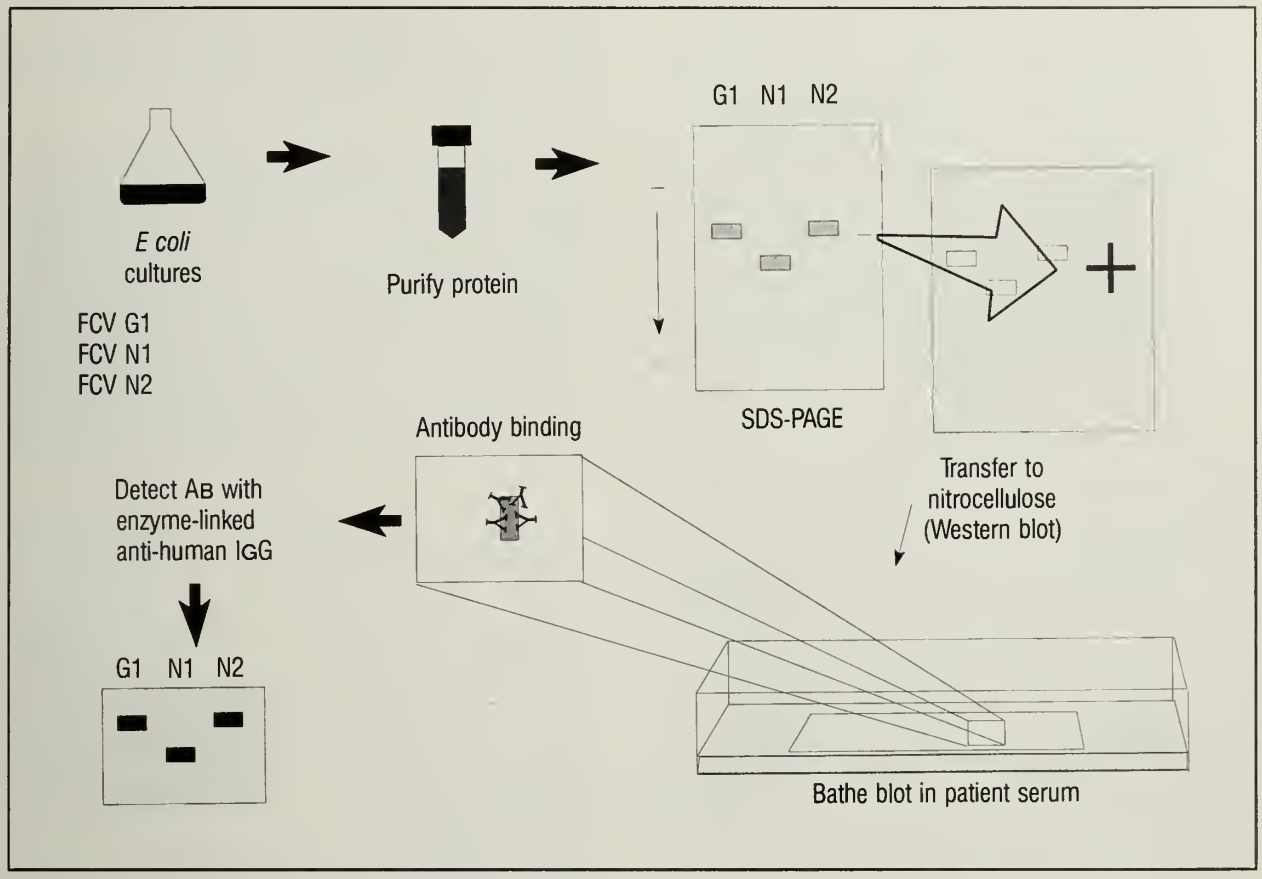

Figure 3.—The recombinant Western blot assay for antibodies to Four Corners virus (FCV) is shown. Proteins produced in *Escherichia coli* are partially purified, then separated according to size by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). The size-separated proteins are then transferred to a nitrocellulose membrane (Western blot). The G1 protein and two different portions of the nucleocapsid protein (designated N1 and N2) are used. Positive serum specimens are those that have antibodies (AB) to both G1 and nucleocapsid protein. IgG = immunoglobulin G

patients were infected with a hantavirus, but also show specifically that they were infected with FCV. Previously there had been no convenient and rapid method to distinguish among related hantaviruses on serologic grounds.[23,24]

The universal presence of IgG and IgM antibodies in patients in the acute stages of the hantavirus pulmonary syndrome suggests that pulmonary injury is a late manifestation of FCV infection. There may, therefore, be an immunologic basis for the pulmonary injury. One model would hold that the breakdown in the endothelial barrier is a result of T cell-mediated attack. Patients who survive the infection are possibly those whose immune responses favor the early production of neutralizing antibodies (T_{H2} response) and not a cytolytic (T_{H1}) response. Although autopsy studies show massive transudation of fluid into alveolar air spaces and pleural spaces, there are only mild interstitial mononuclear cell infiltration and minimal cellular damage.[27]

Unanswered Questions

Many important questions about the hantavirus pulmonary syndrome remain open:

• *Why was the syndrome identified only recently?* Many of the best-known examples of viral "emergence" can be linked to some new exposure of a population to a preexisting pathogen. Viral emergence can follow the incursion by humans into uninhabited terrain or other ecologic derangements that increase their likelihood of exposure to a new agent.[28,29] The genetic sequence of FCV indicates that it is an old virus.[13,14] A case of FCV infection dating back to 1975 was well documented.[17] The finding that genetically related but distinctive FCVs can be detected in patients from a broad geographic range also supports the concept that FCV is old.[13,30]

The working hypothesis held by some is that FCV emerged as a result of large increases in vegetation and the rodent population after a wet winter prompted by an *El Niño* event. The crowding may have facilitated both the transmission of virus among rodents and increased human contact as rodents entered domiciles in search of food. This put humans at risk of disturbing and possibly aerosolizing the rodent excreta that are suspected of harboring virus. A series of cases of the hantavirus pulmonary syndrome in a confined area with a central medical examiner's office led investigators to recognize

the illness and, retrospectively, a number of past cases.

• *How should patients with this syndrome be treated?* Early recognition of the characteristic clinical findings and early antibody testing of patients who manifest those findings probably will benefit them. Prompt admission to an intensive care unit of those patients with low oxygen saturation should also result in lower mortality. Administering antiviral agents may be appropriate, although some suspect that clinical illness arises after the virus is largely neutralized and viremia is already on the decline. Ribavirin has been used in an open-label (uncontrolled) clinical trial. Its use was found to result in lower mortality in a large clinical trial against Hantaan virus in Asia.[31]

• *How is FCV transmitted to humans? What public health measures should be instituted to reduce the incidence of the hantaviral syndrome?* As with hemorrhagic fever with the renal syndrome, it appears that activities that place persons at risk for exposure to rodents and their excreta are associated with the hantavirus pulmonary syndrome.[32] Trapping rodents, handling them, and being in rodent-infested buildings place persons at risk. Rodent trapping as a risk factor is thought to be a marker for exposure to rodent-infested dwellings or buildings. To reduce the risk of exposure to FCV in rodent-infested buildings, the New Mexico Department of Health recommends the trapping of rodents. Trapping can be done safely only if dead rodents are disposed of safely. Dead rodents and their excrement should be sprayed with a disinfectant or a 10% solution of bleach before disposal in an airtight container such as a plastic bag.

There is no evidence for the involvement of an arthropod vector in the transmission of any hantavirus. That issue should be reexamined using the sensitive molecular tools available now, however. The most likely route for transmission of hantaviruses to humans is the introduction of virus to the respiratory tract by aerosols of rodent excreta. Infected rodents are known to excrete infectious Hantaan virus in their urine, feces, and saliva.[33]

• *Do other hantaviruses cause the hantavirus pulmonary syndrome?* During the course of CDC's investigation of the outbreak, workers discovered that one fatal case of the syndrome appears to have been caused by a new hantavirus that is distinct from FCV.[12] That case occurred in Louisiana. It also appears that pulmonary disease is a more common manifestation of infection by known hantaviruses than was previously realized.[34] That all hantaviruses and all hantavirus-related illnesses are now identified seems unlikely. An important goal of future efforts will be to catalogue more thoroughly the incidence and extent of hantaviral illness in North America and elsewhere.

• *Why does the hantavirus pulmonary syndrome develop in so few children?* The youngest patients who have contracted the disease are in the range of 12 to 14 years. Several have survived without the need for mechanical ventilation. It would be surprising if children younger than 12 were not coming into contact with infected rodent excreta or were protected in some way from infection. It is possible, but remains to be proved, that severe pulmonary disease is less likely to develop in younger children with infection by FCV.

Acknowledgments

Many persons at the University of New Mexico School of Medicine and elsewhere facilitated the work of our laboratories during the hantavirus outbreak. Space limitations prevent us from naming them all. Norah Torrez-Martinez, Francesca Chavez-Giles, Carol Morris, and Takashi Yamada, MD, PhD, played especially prominent roles in the development of a serologic test for FCV. Charles Key, MD, PhD, provided crucial support on many levels. The University of New Mexico's Department of Pathology and the Department of Medicine's Infectious Diseases and Pulmonary divisions provided information about the clinical description of the hantavirus pulmonary syndrome. We also benefited from the collective wisdom and contributions of Connie Schmaljohn, PhD; Richard Yanagihara, MD, MPH; C. Y. Kang, PhD; Karl M. Johnson, MD; Gerald Myers, PhD; Kersti MacInnes, MS; and Mack Sewell, ScD. Stuart Nichol, PhD, Kurt Nolte, MD, and Ross Zumwalt, MD, generously provided unpublished data for this manuscript.

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MITERED CORNERS

The world expands to November.
The trees fly far apart
without symmetry,
but in the little house,
in the little house
she fashions words
and one floor down,
he makes windows others will look from,
patiently fitting joints
to suit Pythagoras.

At night when the gray turns black
and settles heavily,
they draw together in the room
reserved for sleep,
lie under cats and quilts,
forming their own soft corner,
joined at an angle
empirically imperfect,
exactly desired.

ELLEN DUDLEY©
Marlboro, Vermont

Articles

Incidence of Digoxin Toxicity in Outpatients

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The incidence of digoxin toxicity among patients in hospitals has declined in recent years. To evaluate whether a similar decline has occurred in ambulatory care, we reviewed randomly selected medical records for 183 outpatients receiving ongoing treatment with digoxin at 10 urban and rural Department of Veterans Affairs Medical Centers in the Rocky Mountain region. The prevalence of traditional risk factors for digoxin toxicity—elevated serum digoxin and serum creatinine levels, hypokalemia, and a new prescription of an interacting drug—was established from computerized laboratory and pharmacy records. Of the 183 patients, 50 (27.3%) had one or more risk factors for digoxin toxicity: serum digoxin levels were elevated in 13.6% of patients in whom a level was obtained, with hypokalemia in 14.3%, elevated creatinine levels in 17.9%, and possible drug interactions in 5.5% of patients over a 1-year period. Nevertheless, digoxin toxicity occurred in only 2 persons (1.1% or 1.4 per 100 patient-years of treatment). We conclude that digoxin toxicity was rare in this group of outpatients, even in persons presumed to be at high risk because of metabolic abnormalities, increased digoxin concentrations, or the use of interacting drugs. The low rate of digoxin toxicity in outpatients parallels the decline in the incidence of toxicity observed in hospital-based studies.

(Steiner JF, Robbins LJ, Hammermeister KE, Roth SC, Hammond WS: Incidence of digoxin toxicity in outpatients. West J Med 1994; 161:474-478)

As long as digoxin has been used in the treatment of congestive heart failure (CHF) and atrial arrhythmias, clinicians have been taught to anticipate a high incidence of digoxin toxicity. Studies published 10 to 20 years ago reported digoxin toxicity in 11% to 30% of patients receiving the drug at the time of hospital admission,[1-5] and the incidence of digoxin toxicity among less acutely ill outpatients has been estimated as 5 cases per 100 patient-years of treatment.[6,7] In more recent reports, however, the incidence of digoxin toxicity had fallen to 5% among patients admitted to hospital with CHF[8] and to 1.1% among closely monitored outpatients in a randomized trial.[9] Most studies that found a high rate of digoxin toxicity were conducted before the widespread use of serum digoxin concentrations to monitor drug treatment and before the development of alternative medications for CHF and atrial arrhythmias. These studies identified risk factors for digoxin toxicity in patients admitted to hospitals, such as elevated serum digoxin levels, hypokalemia, renal impairment, or the prescription of interacting medications.[10] They did not define the predictive value of these risk factors in outpatients, however—that is, the likelihood that digoxin toxicity would actually develop in outpatients with a given risk factor. To determine whether the incidence of digoxin toxicity has declined in ambulatory care practice and to establish the prevalence and predictive value of traditional risk factors for digoxin toxicity in outpatients, we conducted a retrospective cohort study among clinic patients receiving digoxin at ten Department of Veterans Affairs (VA) medical centers in the Rocky Mountain region.

Methods

In December 1988, the VA quality assurance organization, the Medical District-Initiated Peer Review Organization (MEDIPRO), authorized a study of digoxin use in the ten medical centers in VA Medical District 23. These facilities (in Cheyenne, Wyoming; Denver, Colorado; Fort Harrison, Montana; Fort Lyon, Colorado; Fort Meade, South Dakota; Grand Junction, Colorado; Hot Springs, South Dakota; Miles City, Montana; Salt Lake City, Utah; and Sheridan, Wyoming) all provide inpatient acute care and outpatient primary care. Two sites (Denver and Salt Lake City) also provide tertiary referral care and

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ABBREVIATIONS USED IN TEXT

AV = atrioventricular
CHF = congestive heart failure
CI = confidence interval
MEDIPRO = Medical District-Initiated Peer Review Organization
VA = [Department of] Veterans Affairs

are located in major metropolitan areas; the remainder are located in either rural communities or cities of less than 50,000 population.

Data Collection

From a pharmacy-generated list of all outpatients who received one or more digoxin prescriptions in the previous year, 20 patients from each facility were randomly selected for on-site review of medical records, computerized pharmacy profiles, and laboratory data. A trained MEDIPRO quality assurance nurse (S.C.R.) completed the chart reviews between August 1989 and February 1990. The reviewer recorded patient demographics and enumerated all outpatient visits and hospital admissions over the 12 months preceding the date of chart review. Atrial arrhythmias were confirmed as an indication for digoxin therapy only if documented by electrocardiograms obtained during the study year. The presence of CHF was assessed by a validated, 12-point CHF scale based on medical record evidence of symptoms (such as paroxysmal nocturnal dyspnea), abnormalities on a physical examination (for instance, the presence of a third heart sound), and findings from chest radiographs (such as alveolar pulmonary edema) during the study year.[6] Patients with a combination of findings totaling 5 or more points on this 12-point scale were defined as having CHF, a cutoff with a sensitivity of 90% and a specificity of 85% for detecting left ventricular failure as documented by an elevated resting pulmonary capillary wedge pressure.[6] The entire medical record for five patients at each site was reviewed to determine how often patients with no evidence of CHF during the study year had CHF in earlier years, explaining the continued use of digoxin.

Computerized laboratory records from the Decentralized Hospital Computing Program at the ten VA medical centers provided all serum digoxin concentrations, electrolytes, and serum creatinine determinations during the study year. To evaluate the prevalence of commonly accepted risk factors for digoxin toxicity, we identified all patients with serum digoxin levels of greater than 2.6 nmol per liter (2.0 ng per ml), serum potassium levels of less than 3.5 mmol per liter (3.5 mEq per liter), or serum creatinine levels of 176.8 μmol per liter (2.0 mg per dl) or greater. From pharmacy profiles, we identified new prescriptions for quinidine sulfate or gluconate, amiodarone, and verapamil hydrochloride, three medications that predictably and substantially increase serum digoxin levels.[10]

Methods for Identifying Digoxin Toxicity

The chart reviewer recorded all diagnoses of digoxin toxicity noted in the medical record. To identify additional cases of digoxin toxicity that lacked an explicit diagnosis in the chart, we conducted a supplemental chart review for all patients who had an elevated serum digoxin level or who reduced the dosage or stopped taking digoxin during

TABLE 1.—*Clinical Characteristics of Patients With Probable or Possible Digoxin Toxicity*

Patient	Age, yr	Reason for Digoxin Use	Digoxin Dose, mg	Possible Drug Interactions	Digoxin Level, nmol/liter (ng/ml)	Serum Potassium, mmol/liter	Serum Creatinine, μmol/liter (mg/dl)	Symptoms Suggestive of Digoxin Toxicity	ECG Evidence of Digoxin Toxicity	Response to Reduced Digoxin Dosage
Probable toxicity*										
1	67	CHF, atrial fibrillation	0.25	None	4.9 (3.8)	3.8	433 (4.9)	Decreased mental status	Slow atrial fibrillation (rate 30 to 60/min)	Mental status returned to normal; increase in heart rate (80 to 98/min)
2	69	CHF, atrial fibrillation	0.625	None	4.4 (3.4)	4.7	239 (2.7)	Vomiting	Normal	Vomiting resolved
Possible toxicity†										
3	68	CHF, atrial fibrillation	0.25	Newly prescribed verapamil	4.1 (3.2)	4.4	115 (1.3)	None	Slow atrial fibrillation (rate 49 to 51/min)	Increase in heart rate (70 to 86/min)
4	76	None apparent	0.25	None	2.7 (2.1)	4.7	80 (0.9)	Anorexia, weight loss	None	No follow-up data
5	46	CHF	0.25	Long-term amiodarone therapy	2.8 (2.2)	5.1	None	Fatigue	None	No follow-up data
6	69	Atrial fibrillation	0.125	None	None	4.5	80 (0.9)	None	Slow atrial fibrillation (rate 40 to 60/min)	Increase in heart rate (65 to 73/min)

CHF = congestive heart failure, ECG = electrocardiogram

*Patients 1 and 2 were identified as having "probable" digoxin toxicity in the medical record, confirmed by the aggregate opinion of the chart reviewers.
†Patients 3 to 6 were rated as having "possible" digoxin toxicity by two chart reviewers, but as having "probable" toxicity by none.

the study year. Medical records and electrocardiograms for these patients were independently reviewed by a general internist (J.F.S.), a geriatrician (L.J.R.), and a cardiologist (K.E.H.). The reviewers recorded any gastrointestinal, neurologic, or visual symptoms or electrocardiographic findings suggestive of digoxin toxicity—sinus bradycardia, sinus arrest, Mobitz I second-degree atrioventricular (AV) block, complete AV dissociation, AV junctional tachycardia, atrial tachycardia with block, unifocal or multifocal ventricular premature beats, ventricular tachycardia, ventricular fibrillation, atrial fibrillation or flutter with a ventricular response of less than 60 beats per minute, or atrial fibrillation with ventricular premature beats.[1,8] The reviewers also recorded whether symptoms or electrocardiographic abnormalities improved after the reduction or cessation of digoxin therapy. Each reviewer then estimated digoxin toxicity as "probable," "possible," or "unlikely." To reach an aggregate rating, we defined "probable" digoxin toxicity in any case rated as probably toxic by at least one reviewer and as possibly toxic by at least one other reviewer.

Statistical Methods

We calculated the person-years of treatment with digoxin from pharmacy records. The incidence of toxicity was calculated both as the number of toxic events divided by the number of study patients and the number of events divided by the person-years of treatment; 95% confidence intervals (CI) for the latter were determined from a table of exact confidence intervals for binomial proportions.[11] The predictive value of each traditional risk factor was calculated as the proportion of patients with the risk factor at any time during the study year in whom digoxin toxicity developed during that year.[12] Interrater reliability was measured by the kappa (κ) statistic, which corrects the proportion of observed agreement for the amount of agreement expected by chance alone. κ-Values from 0.0 to 0.20 represent "slight" agreement, 0.21 to 0.40 represent "fair" agreement, while 0.41 to 0.60 is "moderate," 0.61 to 0.80 is "substantial," and 0.81 to 1.0 is "almost perfect" agreement.[13]

Results

Of the 200 patients randomly identified for the study, medical records were available for 183 (91.5%). The mean age of the 183 patients was 69.1 ± 9.5 years; 98.9% were male. These patients had 7.1 ± 6.4 outpatient visits to the VA facility during the study year and 0.8 ± 1.3 hospital admissions for all causes. The mean digoxin dose prescribed was 0.20 ± 0.81 mg per day; 17 patients (9.3%) were prescribed doses greater than 0.25 mg per day. In all, 59 patients (32.2%) had electrocardiographic evidence of atrial arrhythmias—atrial fibrillation or supraventricular tachycardia—and 66 (36.1%) had CHF; 36 patients (19.7%) were admitted to hospital for atrial arrhythmias or CHF. Overall, 96 patients (52.5%) had one or both indications for digoxin use during the study year. We completed 48 full chart reviews to assess whether the one-year review underestimated the prevalence of CHF. This condition was present in 17 of these patients (35.4%), of whom 3 had evidence of CHF in previous years, but not during the study period. Thus, the use of the one-year chart review did lead to a modest underestimation of the actual prevalence of CHF in our sample.

The 183 study patients accumulated a total of 141.6 person-years of digoxin treatment during the study year. Only two cases of digoxin toxicity (1.1%; 1.4 per 100 patient-years on the drug; 95% CI, 0.4 to 5.5) were explicitly noted in the medical record. Neither of these patients died of digoxin toxicity. Both patients had increased serum digoxin concentrations and elevated serum creatinine levels at the time of their toxicity; neither had hypokalemia or a possible drug interaction with digoxin. These patients' clinical characteristics are described in Table 1 (patients 1 and 2). Medical records for the supplemental chart review to detect digoxin toxicity were obtained for 37 of the 38 patients (97%) who had serum digoxin concentrations of greater than 2.6 nmol per liter (12 patients) or who had reduced the dosage or stopped taking digoxin (32 patients). The two patients diagnosed with toxic reactions by their clinicians were included in this supplemental review. Reviewer A rated 6 of the 37 patients as possibly toxic and 1 as probably toxic, whereas reviewer B rated 7 patients as

TABLE 2.—*Prevalence of Risk Factors for Digoxin Toxicity*

	Patients With Sufficient Data for Evaluation*		Patients Ever Having Risk Factor†		Patients With ≥30 Days' Duration of Risk Factor†		Patients With Risk Factor(s) Having Probable Digoxin Toxicity	
Risk Factor	No.	%	No.	%	No.	%	No.	%
Possible drug interaction‡	182	99.5	9	5.5	7	3.8	0/9	0.0
Serum digoxin level >2.6 nmol/liter (2.0 ng/ml)	88	48.1	12	13.6	3	3.4	2/12	16.7
Serum creatinine level ≥176.8 μmol/liter (2.0 mg/dl)	145	79.2	26	17.9	14	9.7	2/26	7.7
Serum potassium level < 3.5 mmol/liter	147	80.3	21	14.3	4	2.7	0/21	0.0

*The number of patients in the study = 183.

†Proportions were determined from the total number of patients with measurement of that risk factor.

‡A possible drug interaction was defined as a new prescription of quinidine sulfate or gluconate, verapamil hydrochloride, or amiodarone for a patient already receiving digoxin.

possibly toxic and 2 as probably toxic, and reviewer C rated 2 patients as possibly toxic and 0 as probably toxic. The agreement among reviewers for the combination of possible-probable toxicity was 84% between reviewers A and B, 86% between reviewers A and C, and 76% for reviewer B with reviewer C. Agreement for probable toxicity alone was greater than 95% among all reviewers, due to the rarity of cases. Similar to previous research,[14] κ-statistics for possible or probable toxicity were 0.52 between reviewers A and B, 0.39 between reviewers A and C, and only 0.10 between reviewers B and C. The aggregate rating confirmed the clinical assessment of probable digoxin toxicity in patients 1 and 2 in Table 1. Four other patients were rated as possibly toxic by two reviewers, but as probably toxic by none. These cases are described as patients 3 to 6 in Table 1. Thus, the supplemental review ultimately identified no additional cases of digoxin toxicity.

Because digoxin toxicity was present in only 2 of the 32 patients who reduced the dosage or stopped taking the drug during the study year, we attempted to identify other reasons for the change in digoxin therapy. No reason for decreasing or stopping digoxin therapy was apparent in the medical records of 12 patients. The reasons for the step-down of digoxin in the remaining 18 patients included increased serum digoxin concentrations without evidence of toxicity (7 patients), the substitution of another drug for digoxin (3 patients), symptoms or electrocardiographic changes attributed to digoxin therapy that were not indicative of drug toxicity (3 patients), and a variety of reasons in the remaining 5 patients.

About 80% of patients had serum electrolyte or creatinine measurements during the study year; less than half (48.1%) were monitored with a serum digoxin level. The mean serum digoxin concentration for these patients was 1.3 ± 0.6 nmol per liter (1.0 ± 0.50 ng per ml). Of the study sample, 50 patients (27.3%) had at least one risk factor for digoxin toxicity during the study year, most commonly an elevated serum creatinine level (17.9%) or hypokalemia (14.3%) (Table 2). In most cases, risk factors appeared to be of short duration (Table 2), as only 9.7% of the patients had elevated serum creatinine levels, and 2.7% had hypokalemia on two consecutive determinations 30 days or more apart. Nine patients received new prescriptions for quinidine or verapamil, of whom only two either reduced their digoxin dosage or were monitored with a serum digoxin level within 14 days of starting the interacting drug. The proportion of patients with risk factor(s) in whom digoxin toxicity developed ranged from 0% for patients with hypokalemia (95% CI, 0.0% to 16.1%) or possible drug interactions (95% CI, 0.0% to 33.6%) to 16.7% (95% CI, 2.1% to 48.4%) among those with elevated serum digoxin levels (Table 2).

Discussion

In this study, we found that the incidence of digoxin toxicity among a cohort of outpatients was only 1.4 per 100 patient-years of treatment, lower than in previous reports.[6,7] Although metabolic and pharmacologic risk factors were relatively common, few patients even in these "high-risk" groups actually had digoxin toxicity over a one-year period, in part because these risk factors were often transient. For example, digoxin toxicity occurred in only 16.7% of persons with serum digoxin levels above the usual cutoff level of 2.6 nmol per liter. When potentially interacting drugs were added to the digoxin regimen, the clinicians in this study rarely took the precaution of reducing the digoxin dose or measuring serum digoxin concentrations to identify possible drug toxicity.[15] Nevertheless, digoxin toxicity did not occur in any of the nine persons prescribed a new interacting drug.

Studies done 20 or more years ago identified digoxin toxicity in 11% to 30% of hospitalized patients receiving the drug.[1-5] The most recent epidemiologic study of digoxin toxicity among patients admitted to hospitals observed only 27 cases among 563 patients (5%) with CHF, however.[8] Our study suggests that a similar decline has occurred in the incidence of digoxin toxicity among outpatients. Several explanations for this observation are possible. Clinicians may have become more attentive to evidence of possible toxicity, or they may have been more vigilant in monitoring for and correcting metabolic risk factors. Because previous studies do not report the rate of diagnostic monitoring for patients receiving digoxin, we cannot compare the monitoring practices of these VA clinicians with those of other groups of physicians. Whereas some authorities have advocated routinely measuring serum digoxin levels in asymptomatic patients,[16] others have recommended a more sparing use of serum digoxin concentrations[17]—a strategy followed by the clinicians in our study. These clinicians also maintained serum digoxin levels in the lower end of the therapeutic range, which likely reduced the risk of drug toxicity in the event of sudden metabolic changes or the addition of interacting drugs. The rarity of digoxin toxicity in our study was not due to the use of lower digoxin doses, as many earlier studies also reported average digoxin doses of 0.125 to 0.25 mg per day.[1,3,4] Likewise, digoxin toxicity was not prevented by avoiding drug interactions, as most patients prescribed an interacting drug neither were closely monitored with serum levels nor reduced their digoxin dose.

Limitations

Our study must be interpreted with an awareness of its limitations. First, the number of patients from each facility in our study was relatively small, although our overall sample is likely representative of outpatients cared for in rural and urban VA medical centers in the Rocky Mountain West. Second, by selecting patients from pharmacy records, we identified many who had been receiving digoxin for prolonged periods of time, rather than an "inception cohort" of patients newly prescribed the drug. Nevertheless, our findings should be applicable to the heterogeneous group of new and long-term digoxin users commonly seen in outpatient practice. Third, we identified only cases of digoxin toxicity that occurred within the VA system. If some patients in our sample were treated for digoxin toxicity in non-VA settings, we would have underestimated the true incidence of digoxin toxic-

ity. The financial incentives to obtain care in the VA and the location of many of these VA facilities in rural areas with limited access to other sources of care reduce the possibility of ascertainment bias. Fourth, not all patients in this retrospective study had complete laboratory information, which could lead to an underestimation of the true prevalence of risk factors. A higher prevalence of risk factors would further lower their predictive value and would thus strengthen our conclusion that toxicity was uncommon even when risk factors were present. Finally, many of the patients sampled lacked an obvious reason for digoxin use, implying that they may have had less severe heart disease than the patients of an earlier era. Although we found these patients overall to be at low risk of digoxin toxicity, we also identified a large subgroup unlikely to benefit from taking the drug.

Clinician Assessments of Digoxin Toxicity

Our study confirmed our clinical impression and that of others that experienced physicians often differ in their assessment of the likelihood of adverse drug effects in general and digoxin toxicity in particular.[8,10,18] A failure to recognize the potential for clinical disagreement is an important limitation of earlier studies of digoxin toxicity, which commonly used a single reviewer. The diverse clinical backgrounds of our reviewers may explain the discrepancies in their assessments of the likelihood of digoxin toxicity. The lowest proportion of possibly toxic patients was identified by reviewer C, the cardiologist, accustomed to seeing severely ill patients admitted to the hospital with digoxin toxicity, and the highest proportion was identified by reviewer B, the geriatrician, who was trained to seek subtle manifestations of drug toxicity among outpatients with many symptoms. The interrater agreements (κ statistics) in our study are consistent with other published assessments of adverse drug reactions[18] and quality-of-care appraisals.[14]

In recent years, the benefits of digoxin have been reevaluated as new drugs have been introduced for the treatment of CHF and atrial arrhythmia. A recent meta-analysis of clinical trials of digoxin use in patients with CHF has supported the use of digoxin in patients with impaired systolic left ventricular function.[19] Digoxin withdrawal has also recently been shown to precipitate acute CHF in patients concurrently treated with diuretics and angiotensin-converting enzyme inhibitors.[9] Although clinical trials are lacking, some researchers have recently questioned the benefits of digoxin in atrial fibrillation because it may provide insufficient control of ventricular rate during exercise.[20] The ongoing redefinition of the role of digoxin is likely to lead to a reduced use of the drug. Our study in the community setting, along with other recent evidence,[8,9] suggests that this improvement in the precision of digoxin use is concurrent with a decrease in the risk of digoxin toxicity.

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Articles

Injuries to Occupants in Cargo Areas of Pickup Trucks

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Transporting passengers in the cargo area of pickup trucks is a public health safety issue in the United States. Our study compared crashes involving passengers in the cargo area with those involving passengers in the cab. We obtained data for all injury events of pickup occupants for 1990 from the California Highway Patrol. A total of 702 traffic reports coded as having passengers riding in pickup truck beds involved 1,685 passengers in the cargo area and 865 in the cab. Significantly more events involving passengers in the cargo area occurred in summer in rural areas and were noncollisions than did events with only cab passengers. Crashes with passengers in the cargo area resulted in death in 5% of passengers. Of the drivers, 81% were male and 22% were younger than 20 years. Among the 1,685 passengers in the cargo area, 65% were male, 36% were younger than 15 years, and 30% were ages 15 to 19 years. Passengers in the cargo area were more frequently ejected and more seriously injured than their counterparts in the cab. Legislation to restrict travel in truck beds and the design of restraints for this area are some measures that may reduce the risk of injury.

(Agran P, Winn D, Anderson C: Injuries to occupants in cargo areas of pickup trucks. West J Med 1994; 161:479-482)

Over the past 20 years, the pickup truck has become an increasingly popular vehicle. The number of light trucks registered increased from about 20 million in 1975 to almost 39 million in 1991. Concomitant with this increase in the number of pickup trucks on the roadways was an increase in pickup truck-related fatalities. The number of deaths of occupants of light trucks has increased 72.6% between 1975 and 1991. In 1975, 13.5% of all occupant deaths occurred in light trucks compared with 24.1% in 1991. The fatality rate for occupants of light trucks was 21.53 per 100,000 registered light trucks compared with 15.63 per 100,000 passenger car occupants in 1991.[1]

These statistics confirm that travel in pickup trucks must be addressed as an occupant safety issue. Of particular concern is travel in the cargo area of a pickup truck. The cargo area is a nonpassenger location of the vehicle, and, as such, it is not designed or required to meet safety standards applicable to passenger locations. Seat-belt laws and child passenger safety laws regulating travel in passenger vehicles are not applicable to the cargo area of pickup trucks. In 1991 in the United States, 238 deaths occurred among occupants of the cargo area of pickup trucks.[1] Children aged 0 through 18 years accounted for 50% of the deaths.

An analysis of crash data related to the occupants of pickup trucks, their location in the vehicle, and injury outcomes will provide data needed to more adequately assess the issue of risk to occupants in pickup trucks. Our study compares crashes in which passengers were riding in the cab with crashes in which passengers were riding in the cargo area of a pickup truck and describes the circumstances, drivers, and passengers of those events with cargo area passengers.

Methods

Data

Data for this study were obtained from the 1990 Statewide Integrated Traffic Records System maintained by the California Highway Patrol, Sacramento, California. The Traffic Records System collects and abstracts data from police crash reports for all injury and fatal crashes occurring on public roadways and investigated by any law enforcement agency within the State of California.

The state database lists vans and pickup trucks together as one classification. Pickup trucks were selected from the data by license plate numbers, which reflect the type of vehicle registration. Pickup trucks are registered as commercial vehicles whereas vans are primarily registered as passenger vehicles. The exceptions to these assignments are pickup trucks with a camper shell permanently attached, which are registered as passenger vehicles, and vans without seats behind the driver's seat, which are registered as commercial vehicles.

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For our study, commercially registered vehicles from the van or truck category were selected as a proxy for pickup trucks. Those pickups assigned a passenger-vehicle license plate number were not included in the analysis as these vehicles could not be selected out from all other passenger vehicles. To test the validity of this proxy method, vans or pickup trucks in the database involved in fatal crashes were linked to the pickup trucks in the Fatal Accident Reporting System for the same year, 1990. This system identifies pickup trucks and vans separately. All vehicles were linked by the exact county, date, and time of crash. Model year and driver's age were used to identify the correct vehicle in fatal crashes that involved more than one pickup truck or van. Exact time was used because both systems obtain their data from police crash reports, which list the time. Of the pickup trucks and vans with commercial license plate numbers, 84% were linked to pickup trucks in the Fatal Accident Reporting System. Of these pickup truck records, 85% were matched to the Statewide Integrated Traffic Records System records with a commercial license plate number. Thus, the method selected for the Statewide Integrated Traffic Records System database was thought to be reasonable to obtain data on pickup trucks.

Definitions of age and cause of crash were those used by the California Highway Patrol. Only events involving injury to pickup truck occupants were selected for study. The primary collision factor was that most responsible for causing the collision, as determined by investigating officers.

For this study, seasons were grouped as follows: winter—December, January, and February; spring—March, April, and May; summer—June, July, and August; and fall—September, October, and November. Times of day were grouped into four 6-hour blocks beginning at midnight, 6 AM, 12 noon, and 6 PM. Urban areas included incorporated cities; rural areas included all unincorporated areas.

"Tow-away crash" was the variable used as an indicator of crash severity. "Ejection" included victims who were partially and those who were completely ejected from the vehicle. Collisions included crashes with objects, other vehicles, pedestrians, bicycles, or animals. "Noncollision events" were those events in which no impact occurred with objects, other vehicles, pedestrians, bicycles, or animals. They also included rollovers.

Statistical Methods

Injury crashes involving pickup trucks with passengers in the cargo area first were compared with injury crashes in which there were no passengers in the cargo area. Drivers carrying passengers in the cargo area were characterized and compared with drivers who had not carried passengers in the cargo area. For those vehicles that carried passengers in cargo areas, passengers in the cargo area were characterized and compared with passengers in the cab. Cross-tabulations were analyzed using the χ^2 test for independence.

Results

In 1990 there were 31,908 crashes involving injury or death to a pickup truck occupant. Of these, 31,206 had passengers only in the cab. Of the crashes, 702 were coded as having passengers riding in the cargo area of a pickup truck, involving 1,685 passengers in the cargo area and 865 passengers in the cab.

Comparison of Injuries

Time and location. Seasonal differences were apparent between the two groups ($P < .001$). Cargo area passenger crashes occurred more frequently in summer (34%) and less frequently in winter (15%). Cab-only passenger crashes were almost equally distributed by season (Table 1). Almost half (43%) of the cargo area passenger crashes occurred between noon and 6 PM. The time distribution was significantly different between the two groups, with more of the cargo passenger events occurring between midnight and 6 AM and fewer between 6 AM and noon (Table 1). Significantly more cargo passenger crashes occurred on the weekend (42%) versus cab-only passenger crashes (28%).

A striking difference was noted between the two groups with respect to location of the event: Almost half (43%) of the cargo area passenger crashes occurred in rural communities compared with a third for cab-only passenger crashes (Table 1).

Crash variables. Using tow-away as an indicator of crash severity, we found that 77% of the cab-only passenger crashes were tow-away crashes compared with

TABLE 1.—*Time and Place of Events Involving Injury to Pickup Truck Occupants*

Time and Place	Passengers in Cargo Area (n=702) No.	(%)	Passengers Only in Cab (n=31,206) No.	(%)	χ^2 P Value
Season					
Winter	107	(15)	7,558	(24)	< .001
Spring	158	(23)	8,171	(26)	
Summer	240	(34)	7,866	(25)	
Fall	197	(28)	7,611	(24)	
Time					
6 AM to noon	107	(15)	7,631	(24)	< .001
Noon to 6 PM	303	(43)	12,222	(39)	
6 PM to midnight	192	(27)	8,000	(26)	
Midnight to 6 AM	100	(14)	3,353	(11)	
Day of Week					
Monday	80	(11)	4,583	(15)	
Tuesday	68	(10)	4,167	(13)	
Wednesday	77	(11)	4,209	(14)	
Thursday	74	(11)	4,275	(14)	
Friday	108	(15)	5,197	(17)	
Saturday	150	(21)	4,782	(15)	
Sunday	145	(21)	3,993	(13)	
Community					
Urban	401	(57)	20,966	(67)	< .001
Rural	300	(43)	10,215	(33)	
Unknown	1	(0)	25	(0)	

TABLE 2.—*Crash Variables of Events Involving Injury to Pickup Truck Occupants**

Variable	Passengers in Cargo Area (n=702) No.	(%)	Passengers Only in Cab (n=31,206) No.	(%)	χ^2 P Value
Tow-away crash	471	(67)	24,123	(77)	<.001
Crash type					
Noncollision	120	(17)	1,862	(6)	<.001
Collision (other vehicle)	442	(63)	23,715	(76)	
Other	140	(20)	5,627	(18)	
Unknown	0	--	2	--	
Primary collision factor					
DUI†	129	(19)	6,118	(20)	.653
Unsafe speed	187	(28)	7,994	(27)	
Other	362	(53)	15,877	(53)	
Unknown	24	--	1,217	--	
Fatal crash	32	(4.6)	745	(2.4)	<.001

*The numbers given in the "unknown" categories were not included in the calculation of percentages

†Driving ability is impaired by ("under the influence of") alcohol or drugs.

64% for the cargo area passenger crashes ($P=.001$). Yet, significantly more of the crashes involving cargo area passengers were fatal crashes (4.6% versus 2.4%; Table 2). A significantly greater proportion of the cargo area passenger crashes were noncollision events (17%), compared with 6% for cab-only crashes (Table 2). The primary collision factor did not differ significantly between the two groups; unsafe speed was the most important factor for both groups.

Comparison of Drivers

More than 80% of drivers in both groups were male. Those who carried passengers in the cargo area and were involved in an injury collision were younger; 22% were younger than 20 years compared with 11% for crashes in which no passenger was in the cargo area ($P<.001$) (Table 3). The two groups did not differ with respect to alcohol use. According to the opinion of the officer writing the accident report, more than 75% of the drivers had not been drinking at the time of the crash.

Characteristics of Passengers and Injuries

A significantly greater proportion of passengers in the cargo area were male (65%) and younger than those riding in the cab: 29% were 5 to 14 years old, and 7% were younger than 4 years (Table 4).

The incidence of passenger ejection from the vehicle was significantly higher for those in the cargo area, 25%, versus 4% for those in the cab. Among those in the cargo area of the pickup truck, 64% were injured and 1.2% fatally injured compared with 51% injured and less than 0.5% fatally injured for those in the cab ($P<.001$) (Table 4).

Conclusions

Our study was designed to characterize pickup truck collisions, drivers, and passengers to determine if there were significant differences between events involving passengers in the cargo area and those in which all occupants were in the cab. Our results add to the evidence that travel in the cargo area of pickup trucks is a substantial risk factor for serious injury in a crash compared with travel in the cab. Even with fewer severe (tow-away) crashes and more noncollision events, passengers in the cargo area had a higher proportion of fatalities from crashes than those with only cab passengers. Cargo area passengers also sustained more injuries. The proportion of ejections for passengers in the cargo area was more than six times that for those in the cab. The increased risk of ejection from the cargo area compared with that in the cab has also been documented in other studies, using different databases.[2-6]

Travel in pickup trucks is a problem affecting youth, from the standpoint of both the passengers and the drivers. Of the cargo area passengers, 65% were younger than 20. Those children who were younger than 12 years, unless somehow "secured" or with an adult, would have been in violation of the existing California law regarding travel in the cargo areas of pickup trucks. Children younger than 4 years (7%) by law must travel in child-restraint systems and were in violation of the California Child Passenger Safety Law.[7]

In this sample of crash events, the drivers who carried passengers in the cargo area were younger than those who had no passengers in the cargo area. More than four fifths of all pickup truck drivers were male. In addition to the age and sex of the driver, the results showing that a significantly greater proportion of the

TABLE 3.—*Characteristics of Pickup Truck Drivers in Events Involving Injury to Pickup Truck Occupants**

Driver Characteristic	Passengers in Cargo Area (n=704)† No.	(%)	Passengers Only in Cab (n=32,439)† No.	(%)	χ^2 P Value
Sex of driver					
Male	570	(81)	26,625	(82)	.445
Female	132	(19)	5,723	(18)	
Unknown	2	--	91	--	
Age of driver, years					
1-14	0	--	27	(0)	<.001
15-19	156	(22)	3,527	(11)	
20-29	233	(33)	11,747	(36)	
≥ 30	315	(45)	17,138	(53)	
Alcohol					
Not been drinking	548	(81)	25,049	(81)	.114
Drinking not DUI‡	30	(4)	948	(3)	
DUI	89	(13)	4,482	(14)	
Drinking but impairment unknown	4	(2)	477	(2)	
Unknown	13	--	1,483	--	

DUI = driving under the influence

*The numbers given in the "unknown" categories were not included in the calculation of percentages.

†Numbers are greater than the number of crashes because some events involved >1 pick-up truck driver.

‡Driver had been drinking but not under the influence of alcohol.

TABLE 4.—*Characteristics of Passengers Involved in Injury Events With Cargo Area Occupants (n = 704 Pickup Trucks)**

Variable	Cargo Area Passengers (n = 1,685) No.	(%)	Cab Passengers (n = 865) No.	(%)	χ^2 P Value
Gender					
Male	1,090	(65)	429	(50)	< .001
Female	586	(35)	429	(50)	
Unknown	9	- -	7	- -	
Age, years					
0-4	117	(7)	81	(9)	< .001
5-14	497	(29)	96	(11)	
15-19	500	(30)	235	(28)	
20-29	306	(19)	217	(25)	
≥ 30	237	(14)	219	(26)	
Unknown	28	- -	17	- -	
Ejection					
Yes	419	(25)	38	(4)	< .001
No	1,266	(75)	827	(96)	
Outcome					
Death	21	(1.2)	4	(0.5)	< .001
Injury	1,071	(64)	442	(51)	
No injury	593	(35)	419	(48)	

*The numbers in the "unknown" categories were not included in the calculation of percentages.

crashes with passengers in the cargo area occurred during the summer and on weekends suggests further that it is an adolescent and male issue involving, perhaps, recreational use of the vehicle.

Our study is limited by the underreporting of noncollision events. Many of these, because they are single-vehicle events and involve no vehicle damage, are not reported to police agencies.[8,9] A second limitation is that the injury scale used in police data is a crude measure of injury severity. Therefore, we were only able to analyze the data by injury, the absence of injury, or death.[10] Patterns of injury and severity could not be determined. We did not have exposure data or information on the reasons why passengers were in the cargo area, the conditions under which they were there, and the purpose of the trip.

Discussion

The issue of occupant travel in the cargo area of pickup trucks must be more fully addressed for three reasons: over the past decade, sales of pickup trucks have greatly increased; the cargo area is not designed to carry passengers; and the safety of occupants in designated passenger areas has been improved by laws on using seat belts and restraints.

State laws addressing travel in the cargo area of pickup trucks vary considerably.[11] Only Minnesota, New Jersey, New Mexico, and California prohibit travel in the cargo area of unenclosed pickup trucks. A few states restrict travel in the open cargo area under certain conditions. In contrast, many states have regulations regarding securing animals in the cargo area of pickup trucks.

Studies that document the hazards of travel in the cargo area of pickup trucks can convince the public as well as legislative bodies and policymakers to impose restrictions on this type of travel. In keeping with the American Academy of Pediatrics policy statement, children through 18 years of age should be prohibited from traveling in this nonpassenger location.[12] Manufacturers and salespersons ought to warn consumers about the dangers of travel in the cargo area of pickup trucks and the increased risk of ejection and inform them that the cargo area is not designed for passengers and does not meet standards for passenger compartments of motor vehicles. There is no safe, crash-tested means of travel in the cargo areas of pickup trucks. Public policy measures aimed at eliminating travel in the cargo areas of pickup trucks, as well as design features to provide safe passenger compartments in pickup trucks, will reduce the health care costs and human tragedy related to travel in the cargo areas of pickup trucks.

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Articles

Prenatal Substance Use in a Western Urban Community

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To assess the extent of prenatal substance use in a predominantly white population in an urban area of the western United States and to develop a risk profile for this population, a cross-sectional prevalence study was done. Prenatal clinics (10 public and 10 private) anonymously recorded demographic information about and collected aliquots of routinely obtained urine specimens from women during prenatal visits. Urine specimens were screened by enzyme immunoassay for amphetamines, marijuana, cocaine, opiates, and ethanol. Of the 935 women screened, 92 (9.8%) had urine specimens positive for one or more of these substances. Urine screens were positive in 56 (10.0%) of 562 women attending private clinics and 36 (9.6%) of 373 women attending public clinics. Only 7 of the 935 women (0.7%) had screens positive for cocaine. Ethanol was the most frequently detected substance in the private clinic group (6.4%), whereas marijuana was most common among women attending public clinics (5.1%). Although substance use in this group of pregnant women occurs at a lower rate and a different pattern from those found in other more densely populated areas, the rate is high enough to be of concern to all prenatal care professionals, who should incorporate substance use history taking and selective urine drug screening into their routine prenatal practices.

(Buchi KF, Varner MW: Prenatal substance use in a western urban community. West J Med 1994; 161:483-486)

Our 1991 study of the prevalence of substance use among parturient women in Utah showed that the rate of substance use is lower among pregnant women in Utah than among inner-city pregnant women from other locations; that cocaine was detected at delivery at a much lower rate than reported from inner-city hospitals; and that alcohol is the predominant substance of abuse in our parturient patients.[1] To further determine the extent of substance use during pregnancy in Utah's predominantly white population and to develop a risk profile of prenatal substance use in this group, a second prevalence study based in prenatal clinics was done.

Subjects and Methods

During the summer of 1992, urine specimens and demographic information were anonymously collected from women at ten public and ten private prenatal clinics. All public clinics along the Wasatch Front, a four-county area of high population density, served as study sites. Voluntary participation by private clinics was solicited, and sites were selected based on the volume of prenatal visits and geographic distribution along the Wasatch Front.

Clinic staffs were instructed to collect urine specimens and nonidentifying demographic information on all women who sought prenatal care during the study period, regardless of week of gestation. After the initial collection period, specimens were collected from women only during their first prenatal visit to ensure an adequate number of first-trimester specimens for statistical analysis. Nonidentifying demographic information collected for each specimen included age, race or ethnicity, insurance status, zip code of home address, parity, week of gestation, and whether the woman was known by her care provider to have used tobacco, alcohol, or social drugs since her last menstrual period. All specimens were delivered to a laboratory certified by the National Institute on Drug Abuse and screened anonymously by enzyme immunoassay (Syva EMIT Drugs of Abuse Reagent System, Palo Alto, California) for amphetamines (cutoff level, 150 ng per ml), marijuana metabolites (20 ng per ml), cocaine metabolites (150 ng per ml), methadone (150 ng per ml), opiates (150 ng per ml), and ethanol (10 mg per dl). The EMIT system, the enzyme immunoassay method most frequently used in the United States,[2] has moderate to good sensitivity and specificity—a false-positive rate of 3% to 5%.[3] Urine specimens positive for amphetamines were subjected to a second test to separate illicit amphetamine from over-the-counter amphetamine analogues such as

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TABLE 1.—*Prevalence of Substance Use Among Women in Prenatal Clinics, Northern Utah*

Substance	Entire Sample (n=935) No. Positive	(%)	Private Clinics (n=562) No. Positive	(%)	Public Clinics (n=373) No. Positive	(%)
Ethanol	49	(5.2)	36	(6.4)	13	(3.5)
Marijuana	29	(3.1)	10	(1.8)	19	(5.1)
Opiates	15	(1.6)	11	(2.0)	4	(1.1)
Cocaine	7	(0.7)	1	(0.2)	6	(1.6)
Amphetamines	1	(0.1)	1	(0.2)	0	(0.0)
Any of above	92	(9.8)	56	(10.0)	36	(9.6)
Positive urine,* negative history†	75	(8.0)	49	(8.7)	26	(7.0)
Negative urine, positive history	80	(8.6)	25	(4.4)	55	(14.7)
Positive urine, positive history	17	(1.8)	7	(1.2)	10	(2.7)
Positive prenatal substance use	172	(18.4)	81	(14.4)	91	(24.4)

*Urine screen is positive for illicit drugs, ethanol, or both.
†History for the use of alcohol or social drugs since last menstrual period is negative or unknown.

pseudoephedrine or phenylpropanolamine. The opiate screen did not differentiate between heroin and prescription pain relievers that contain opiates.

Statistical analysis included χ^2 tests for univariate analysis of discrete variables, Student's t test for univariate analysis of continuous variables, and logistic regression for multivariate analysis, using the Statistical Package for the Social Sciences (SPSS Inc, 1989).

Results

During the study period, urine specimens were obtained from 935 of 957 (97.7%) women who received prenatal care. The women from whom urine specimens were not obtained did not differ from the other women in age, race or ethnicity, insurance status, marital status, parity, clinic site, or whether they had a recorded history of tobacco, alcohol, or drug use since their last menstrual period. Of the 935 women from whom urine specimens were obtained, the mean age was 24.7 years; 82.6% were white, 48.2% had private insurance, and 69.7% were married. Of the 935 specimens, 101 tested positive for ethanol, marijuana, opiates, cocaine, or amphetamines in 92 urine specimens, giving a prevalence rate for these substances of 9.8%.

Ethanol positivity in the urine was more prevalent among women attending private clinics than among women attending public clinics ($P = .05$) (Table 1). Marijuana and cocaine were detected more frequently among those in public clinics ($P = .004$ and .013, respectively). Opiate positivity did not differ significantly between the two groups.

When the number of women with a history of alcohol or social drug use since the last menstrual period but with negative urine screens is added to the number of women with positive urine screens, the prevalence rate for women with prenatal substance use rises from 9.8% to 18.4% for the entire sample (Table 1). Women in public clinics had a prevalence rate 1.7 times higher than that for women in private clinics (24.4% versus 14.4%). Table 2 indicates the method of identifying prenatal substance use in pregnant women in both public and private clinics.

In private clinics, women identified as having used substances of abuse prenatally—those with positive histories or positive drug screens for illicit substances or alcohol—were more likely than women with negative histories and screens to have Medicaid or no insurance ($P = .01$), to be unmarried ($P = .001$), and to have a history of tobacco use since the last menstrual period ($P = .0001$). When these characteristics that are statistically significant by univariate analysis are entered into a forward-stepwise logistic regression model, only a positive history of tobacco use remained significant with an odds ratio of 0.11 (95% confidence interval, 0.08 to 0.15).

In public clinics, women identified as positive for prenatal substance use differed in the measured variables from women identified as negative for substance use only in that the women who were positive were more likely to have had a recent history of tobacco use ($P = .0001$).

Women attending public clinics for their first prenatal visit were more likely to have positive histories or drug screens for prenatal substance use than women attending private clinics for their first visit, especially if their first visit was after the first trimester (Table 3). A history of tobacco use since the last menstrual period was the only demographic characteristic that varied significantly between first-visit women in public clinics who were identified as positive for prenatal substance use and those who were identified as negative. Women attending private clinics for their first prenatal visit who were positive for prenatal substance use were more likely to have Medicaid or no insurance ($P = .04$) and to

TABLE 2.—*Identifying Substance Use During Pregnancy by Urine Screen or History*

Identifying Method	Women Positive for Prenatal Substance Use: Public Clinics No.	Public Clinics (%)	Private Clinics No.	Private Clinics (%)
Urine screen alone	26	(29)	49	(60)
History alone	55	(60)	25	(31)
Both history and urine screen	10	(11)	7	(9)
Total	91	(100)	81	(100)

have used tobacco since the last menstrual period ($P = .0001$) than women who were negative for prenatal substance use.

In the entire cohort, the prevalence of illicit substances—opiates, cocaine, amphetamines, and marijuana—did not vary significantly by trimester, even when the specimens were categorized by clinic site. Ethanol positivity in private clinics was less prevalent during the first trimester (2%) than during the second (8%) and third (8%) trimesters ($P < .05$). There were no significant differences between the trimesters for prevalence of ethanol positivity in public clinics.

Women attending private clinics in urban and suburban northern Utah differed demographically from those attending public clinics. Women from private clinics were similar to the overall parturient population along the Wasatch Front in race or ethnicity and marital status, whereas women attending public clinics differed significantly from that population. Public clinics served women who were younger, more likely to be of minority status, more likely to have Medicaid or no insurance, and more likely to be single and primiparous than women in the private clinic cohort ($P = .0001$). The use of tobacco, alcohol, or social drugs since the last menstrual period was also more likely to be detected by clinic staff in women in public clinics ($P = .0001$).

Zip code data were analyzed to determine if there were regional differences in the prevalence of use of illicit drugs and alcohol. No statistically significant differences were found when comparing prevalence rates among the four counties of the Wasatch Front.

Discussion

The prevalence of substance use based on urine screens among pregnant women at delivery has been reported to be 20.5% at a tertiary obstetric center in Sacramento, California,[4] and 24% at an inner-city hospital in New York City.[5] Published rates among women attending prenatal clinics vary from 11.0% in a cohort of mostly white women from rural Missouri[6] and 11.0% among Alabama women attending public clinics[7] to 14.8% among women attending for their first prenatal visit at private and public clinics in Pinellas County, Florida.[8] Our survey methods were similar to those of the Florida study, except that we used a lower cutoff level for the detection of ethanol and we did not limit the screens to the first prenatal visit. Both our overall rate of urine drug positivity (9.8%) and the rate of positivity among women at their first prenatal visit (8.6%) were lower than those in the Florida study. The rates of urine positivity among women attending private and public clinics were similar in Utah. This is consistent with the findings in the Pinellas County study.[8] When looking specifically at women presenting for their first prenatal visit, however, the rate of positivity among women attending public clinics is three times higher than the rate found among women attending private clinics. We also found a different drug-use pattern than in the Florida study. In Utah, alcohol and marijuana were the two most commonly detected drugs, with cocaine detected very infrequently. In Pinellas County, marijuana and cocaine were detected most frequently. Both Pinellas County and the Wasatch Front are considered urban areas—population density greater than 100 persons per square mile—and have predominantly white populations. The four counties involved in our study are much less densely populated—132 to 963 persons per square mile[9]—than Pinellas County, which has 3,100

TABLE 3.—*Prevalence of Substance Use Among Women Attending Their First Prenatal Visit*

Method	Private Clinics: 1st Trimester (n=104) No. Positive	(%)	Private Clinics: After 1st Trimester (n=31) No. Positive	(%)	Public Clinics: 1st Trimester (n=37) No. Positive	(%)	Public Clinics: After 1st Trimester (n=40) No. Positive	(%)
Positive urine,* negative history†	4	(4)	2	(6)	2	(5)	6	(15)
Negative urine, positive history	7	(7)	1	(3)	3	(8)	6	(15)
Positive urine, positive history	1	(1)	0	(0)	1	(3)	3	(8)
Positive prenatal substance use	12	(12)	3	(10)	6	(16)	15	(38)

*Urine screen is positive for illicit drugs, ethanol, or both.
†History for the use of alcohol or social drugs since last menstrual period is negative or unknown.

persons per square mile. The rate of urine positivity for cocaine, amphetamines, marijuana, and ethanol in this study, 8.5%, is not statistically different from the rate of 7.8% obtained in our first study, which screened women at delivery.[1] The prevalence rates as determined by urine screens obtained from the two Utah cross-sectional studies indicate that substance use among pregnant women in this community is lower than that reported in other urban areas and may be more representative of other less densely populated communities.

A limitation of using a one-time urine screen to determine the use of substances of abuse is that only women who have used an illicit substance or ethanol in the recent past will test positive, but women who have abstained for a short period of time will go undetected. In our study, clinic staff recorded whether there was a history of substance use since the last menstrual period. The prevalence of substance use among pregnant women in northern Utah rises to a worrisome rate of 18.4% when this historical information is taken into consideration.

Two of the principal purposes of this study were to determine the most useful method for prenatally detecting substance use in this group and to gather information to develop a risk profile for substance use. Proportionately more women attending public prenatal clinics were identified through history as having exposed their fetuses to substances of abuse than women attending private clinics, despite the fact that the rate of urine positivity for alcohol, drugs, or both was similar at both clinic sites. Public clinics in Utah use a state health department prenatal form that has a specific area devoted to substance use history. The answers to the history questions on substance use are used in the ongoing risk assessment of women receiving prenatal care at public sites. Private clinics do not use this form consistently and may rely on personal characteristics of a woman to determine whether questions are asked regarding substance use. Our results, though, did not identify particular characteristics that could differentiate between users and nonusers in this group of pregnant women except a history of tobacco use. Other investigators have commented on the poor reliability of a routine medical history to predict positivity of a urine drug screen.[5,10] We found that in private clinics, 88% of women with a positive urine screen had negative histories of substance use. In public clinics, 72% of women with positive urine screens had negative histories of substance use. Even though the drug history-taking missed many of the women with positive urine screens, the difference between the prevalence of positive histories for substance use at both clinic sites suggests that incorporating specific questions regarding substance use into routine prenatal care will increase the likelihood of detecting substance use problems.

Relying solely on a substance use history, however, would have missed a substantial number of the substance users who were identified through urine screens, even at public clinics where substance use histories are routinely taken. Investigators have recommended that urine toxicologic screens be incorporated into routine prenatal care work in communities where the rates of urine positivity for illicit substances, especially cocaine, are substantially higher than those found in northern Utah.[5,10] Some have commented that routine urine drug testing may not be cost-effective in areas of relatively low prevalence.[10] This was the case in a private obstetric group in Colorado that had a rate of cocaine positivity similar to that in our community, which led to the recommendation that taking a substance use history and the results of a physical examination be the initial drug screen in pregnant patients.[11] The relatively low rates for illicit substances on urine screens among pregnant women in our community when compared with inner-city areas do not justify a recommendation for routine prenatal drug screening for all women. A selective use of urine drug screens in conjunction with taking routine histories of substance use may help to identify substance-using women. Our study found only one characteristic, a history of tobacco use, to be significantly related to substance use. Further research that will gather more detailed information about these women is needed to develop a more discriminating risk profile.

Our study further confirms that substance use among pregnant women in this western, urban, white population occurs at a lower rate and in a different pattern from that found in more densely populated urban areas, especially in regard to cocaine use. The rate is high enough, however, to prompt all providers of prenatal care to incorporate substance use histories and selective urine drug screening into their routine prenatal practices. Emphasis on asking about and testing for substance use during prenatal visits will help identify pregnant women with recent substance use and increase the opportunities for education and intervention.

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Conferences and Reviews

Colorectal Cancer

A New Look at an Old Problem

Discussant
NEIL W. TORIBARA, MD, PhD

This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

HOMER A. BOUSHEY, MD*: *Colorectal cancer is a highly prevalent health problem. The combined factors of a long natural history, familial susceptibility, and endoscopic accessibility of this malignant disorder and its precursor lesions offer a unique opportunity to understand the molecular genetics involved in the pathogenesis of colorectal cancer and to develop techniques and strategies for its early detection and prevention. Recent progress toward the realization of these goals has been exciting and is reviewed in this conference by Neil Toribara, MD.*

NEIL W. TORIBARA, MD, PhD†: Colorectal cancer is a major health problem in the United States. Cancer is the second leading cause of death in this country, behind only atherosclerotic cardiovascular disease, and colorectal cancer is the second leading cause of death from malignant neoplasms. This year an estimated 157,000 cases will be diagnosed and 56,000 deaths will result from colorectal cancer. The lifetime probability of colon cancer developing is approximately 1 in 15, or about 6%. Despite major advances in diagnostic and therapeutic technology, new understanding of some of the molecular changes occurring during colorectal carcinogenesis, and the inclusion of some form of screening in the health maintenance programs of many patients, the mortality from this disease remains high at slightly less than 50%.[1]

In this discussion I will briefly outline our current understanding of etiologic factors in colorectal cancer and the prognosis of this disease with current therapy and follow with a more detailed account of two areas in which important advances are being made, molecular pathogenesis and early detection.‡

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‡See also the editorial by D. J. Ahnen, MD, "How to Capture a Revolution," on pages 523-525 of this issue.

Etiologic Factors

Epidemiologic and experimental studies suggest that factors involved in the development of colorectal cancer can be divided into exogenous and endogenous categories. The exogenous factors include environmental toxins and dietary components, and the endogenous factors include oncogenes or tumor suppressors and possibly metabolic abnormalities.

The effect of environmental elements is evident when the rate of colorectal cancer development is examined in populations migrating from a region with low rates to a region with a high rate.[2] Figure 1 shows the incidence of colon cancer in the Japanese population and the United States white population at age 60.[2,3] The issei (the emigrants to the United States) had an incidence that is higher than that of their Japanese counterparts, but considerably lower than that of the white population. But the nisei, the first generation to be born and raised in the United States, acquired essentially the same incidence of colorectal cancer as that of the indigenous whites. Similar statistics have been reported in European emigrants to the United States and Polish emigrants to Australia.[4] The rapid acquisition of this higher rate of colorectal cancer development is almost certainly due to environmental or dietary factors, or both.

A number of dietary elements have been suggested, some of which are listed in Table 1. The protective effects of fiber may be a combination of decreasing the transit time of intestinal contents, diluting and binding of possible toxins, and complex alterations of the bacterial biochemical milieu. These have the net effect of decreasing the amount of biologically active possible carcinogens available and their contact time with the bowel mucosa.[5] High fat intake has also been associated with an increased risk for colorectal cancer, possibly by inducing increased amounts of bile acid synthesis. These bile acids are metabolized by bacteria in the colon to secondary bile acids that, although they themselves are

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ABBREVIATIONS USED IN TEXT

FAP = familial adenomatous polyposis
FOBT = fecal occult blood test
HNPCC = hereditary nonpolyposis colon cancer

not carcinogenic, potentiate the effects of carcinogens.[6] Experimental evidence suggests that calcium,[7] folate,[8] fish oil,[9] and vitamins A, C, and E[10,11] may have protective effects against the development of colorectal cancer. Recently reports have suggested that patients on a low-dose aspirin regimen had a substantially lower rate of colon cancer development than controls.[12,13] This, along with reports of the efficacy of sulindac in causing polyp regression in some patients with familial polyposis,[14] suggests that an inhibition of prostaglandin synthesis may protect against the development of cancer.

The endogenous or genetic factors vary widely in their contribution to the genesis of colorectal cancer. In some polyposis syndromes and cases of hereditary nonpolyposis colon cancer (HNPCC) that include kindreds with colon cancer alone (Lynch syndrome type I) and colon cancer as part of a spectrum of malignant neoplasms (Lynch syndrome type II), the colorectal cancer inheritance is autosomal dominant and the genetic contribution is clear.[15,16] Even in patients with relatives who have had either colon cancer or adenomatous polyps, however, the risk of colorectal neoplasms developing is greater than in an age-matched population, depending on the number of relatives, the degree of relatedness, and the age of onset of the disease in those relatives.

Prognosis of Colorectal Cancer With Current Therapy

Figure 2 shows the distribution of colorectal cancers. Over the past several decades, a relative shift has occurred in the distribution of these cancers toward the proximal colon that has made progressively fewer of these lesions accessible to digital rectal or rigid sigmoidoscopic examination. About 60% of colon cancers are distal to the splenic flexure and thus within the reach of a 60-cm flexible sigmoidoscope.[17] In patients with HNPCC, however, about 70% of the cancers will be proximal to the splenic flexure, making flexible sigmoidoscopy inadequate as a surveillance method.

The prognosis of patients with colon cancer depends on the stage at diagnosis. The most commonly used systems are modifications of the staging proposed by Cuthbert Dukes in 1932. Table 2 shows the Turnbull modification[18] of the Dukes' staging system for colorectal carcinomas along with five-year survival rates.[19-22] A malignant lesion confined to the mucosa is known as carcinoma in situ. Because there are no lymphatics within the mucosa, these lesions are thought to have no metastatic potential, and therefore surgical or endoscopic excision (when possible) of these lesions is considered to be curative. Invasive cancers are staged according to their degree of penetration through the bowel wall (stages A and B), spread to local lymph nodes (stage C), and the presence of distant metastases (stage D). The survival statistics for patients with stage C2 or D lesions may improve in the future, however. Recent studies showed that about 65% of patients with stage C lesions treated with surgery and the chemotherapeutic combination of fluorouracil and levamisole hydrochloride were disease-free five years after diagnosis.[23] A number of studies have reported success in surgically treating isolated hepatic and pulmonary metastases. Only a few patients with stage D disease are candidates for such treatment, however.[24] Studies have not shown a significant advantage in treating rectal cancers with fluorouracil and levamisole, and patients are usually given irradiation combined with adjuvant fluorouracil.

TABLE 1.—*Possible Dietary Components in Colorectal Carcinogenesis*

Protective Effects	*Increases Risk*
Fiber	Fat intake
Calcium	Folate deficiency
Salicylates	Carcinogen ingestion
Vitamins A, C, and E	

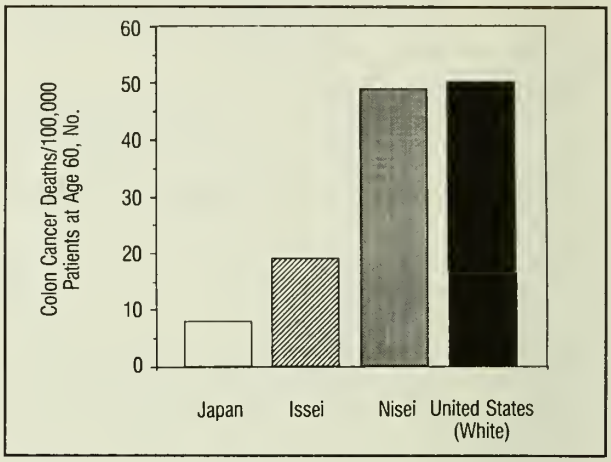

Figure 1.—Japanese emigrants to the United States (issei) have a higher incidence and mortality from colon cancer than the Japanese in Japan. The first generation born and raised in the United States (nisei) has acquired the same colon cancer incidence and mortality as the US white population (data from Haenszel and Kurihara[2]; adapted by permission from Daniel Podolsky, MD, and Milner-Fenwick Company[3]).

Pathogenesis of Colorectal Cancer

Carcinogenesis is thought in most cases to be a multistep process, with the first step involving the acquisition of a heritable mutation in DNA.[25] This alters the growth characteristics of a previously normal cell, which, in the case of colorectal cancer, results in an abnormally proliferating focus of cells that is morphologically identifiable as an adenomatous polyp. These abnormally proliferating but still "benign" cells are predisposed to undergoing further genetic changes that may result in cells with an overtly malignant phenotype. This multistep theory of colorectal carcinogenesis implies two major concepts: that colorectal adenomas are premalignant lesions and that malignant lesions should have more genetic abnormalities than premalignant lesions. I will explore each of these points briefly.

TABLE 2.—*Modified Dukes' Classification for Colorectal Cancer* With 5-Year Survival by Stage†*

Dukes' Stage	*Extent of Tumors*	*5-Year Survival, %*
A	Limited to submucosa	90-95
B	Into muscular layers of the colon	
B1	Into muscularis propria; no nodal metastases	90
B2	Through serosa; no nodal metastases	75
C	Regional nodal metastases	
C1	1-4 regional nodes	65
C2	>4 regional nodes	42
D	Distant metastases	>5

*From Turnbull.[18]

†From Newland et al,[19] Turnbull et al,[20] and the Gastrointestinal Tumor Study Group.[21] Some surgical series report different survival figures (Moertel et al[22]).

The first point is the so-called adenoma-carcinoma hypothesis. Evidence from epidemiologic studies of sporadically occurring colonic adenomas and carcinomas and familial polyposis syndromes strongly suggests that adenomas precede carcinomas by five to ten years.[15,26] Histologic studies show a continuum of increasing polyp size and dysplasia from simple tubular adenomas to malignant neoplasms that correlates well with an increasing risk of containing malignant foci (Table 3).[29] These findings, along with the frequent coexistence of adenomatous and malignant tissue within the same lesion, add considerable weight to this hypothesis.[27-29]

Thus, if colorectal adenomas are precursors to carcinoma, then proving this hypothesis would appear to be relatively straightforward; that is, the removal of adenomas should markedly decrease the incidence of colorectal cancer. The idea, however, that adenomas are premalignant lesions has gained such strong support that it is considered unethical to have a study group in which adenomas are not removed. As a result, investigators have had to use historical data to determine the expected number of colon cancers in a given population as a control group. Patient selection in these studies has also been criticized. With that in mind, studies have shown that removing all polyps decreases the expected rate of rectal cancer development by 70% (polypectomies during rigid sigmoidoscopy)[30] and that of colorectal cancer by 57% to 87% (polypectomies during total colonoscopy).[31] Thus, the evidence strongly supports the theory that adenomas are premalignant lesions. Malignant lesions arising in patients with inflammatory bowel disease, the flat adenoma syndrome,[32] and HNPCC may not have a clear adenomatous polyp phase. These conditions make up a small percentage of the total number of cases of colorectal cancer, however.

Molecular Genetic Events in Colorectal Carcinogenesis

Molecular studies of the roles played by oncogenes and tumor suppressors during cell replication clearly indicate that replication is controlled at several levels extending from the external cellular milieu to the innermost parts of the nucleus. Because the multistep theory of carcinogenesis predicts that as a cell proceeds toward malignancy, a number of genetic alterations will occur, it follows that these alterations would occur in proteins that are control points for cellular replication.[25] A process as vital—and, if uncontrolled, possibly lethal—as cell replication would be expected to have controls at several levels, and the most commonly held view is that the key proteins at these control points are proto-oncogenes and tumor suppressors. The multitude of proto-oncogenes or tumor suppressors currently known suggests that the number, chronology, and identity of these genetic alterations need not be the same in each neoplasm, but that, overall, malignant lesions should have more mutations than premalignant lesions. Because of fiberoptic technology, it has become relatively easy to obtain fresh specimens from all stages of colorectal cancer development, making studies of the genetic changes occurring during carcinogenesis possible.

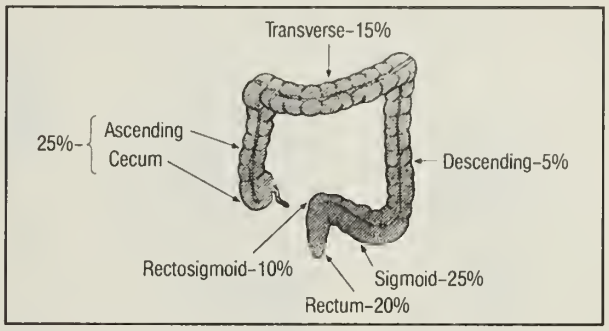

Figure 2.—The schematic shows the distribution of colorectal cancers.

In a landmark study, Vogelstein and co-workers examined the frequency of several genetic alterations known to be present in many colon cancers, that is, *ras* gene mutations and chromosomal deletions on 5q (adenomatous polyposis coli gene, which is mutated in both familial adenomatous polyposis [FAP] and Gardner's syndrome), 18q (*DCC* ["deleted in colon cancer"]), and 17p (*P53*), and correlated these alterations with their "position" in the adenoma-carcinoma sequence.[33] Their data suggested that a general chronologic order of genetic alterations can be made—that is, 5q, *ras*, 18q, 17p (Figure 3),[33,34] although the order was by no means invariable; and that a strict chronologic order of genetic alterations is not as important as their accumulation in the development of colorectal cancer (Figure 4). Subsequent work in experimental systems has suggested that correcting the defects in tumor suppressor genes will inhibit tumorigenicity.[35,36]

Because knowledge regarding the genetic changes involved in colorectal carcinogenesis has been accumulating so rapidly, it is easy to forget that the story is far from complete. Recently regions on chromosomes 2 and 3 have been linked with most of the HNPCC kindreds.[37-41] Hereditary nonpolyposis colorectal cancer is strongly associated with a phenotypic pattern of genomic instabil-

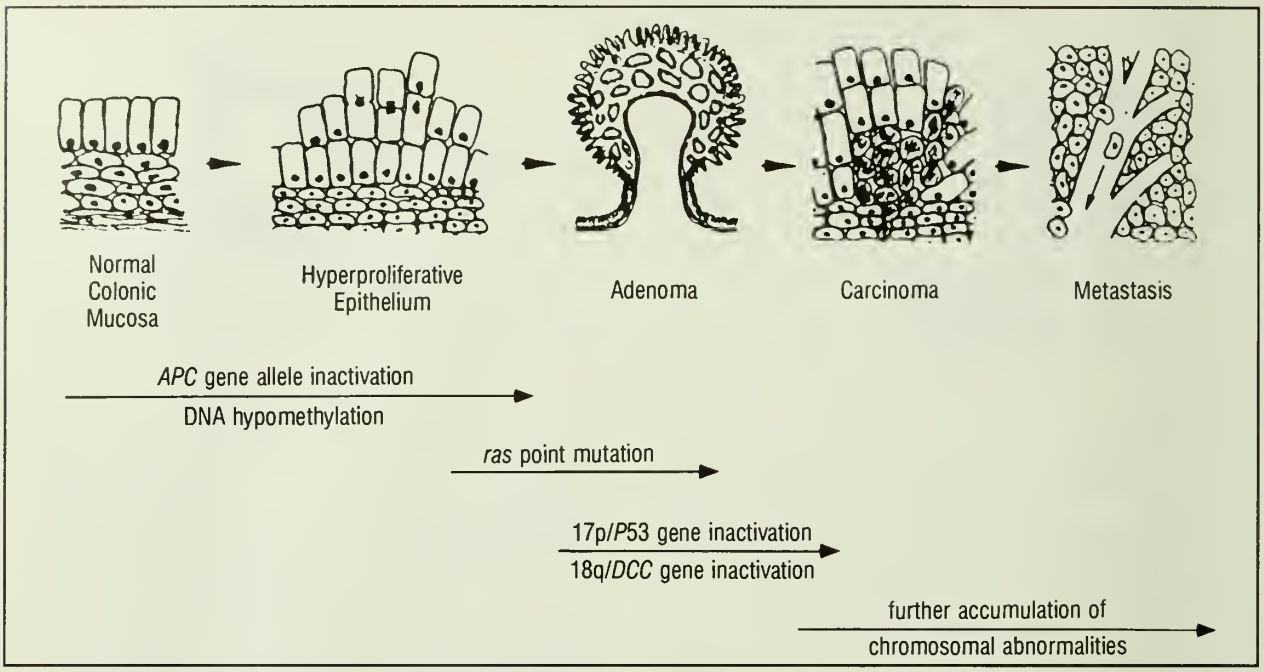

Figure 3.—Genetic alterations are shown during the adenoma-carcinoma sequence. Although this graph shows the most common chronology, the accumulation of abnormalities rather than their specific order is probably more important in developing the malignant phenotype (from Vogelstein et al[33]; reproduced from Bresalier and Toribara[34] with permission from the authors, WB Saunders Company, and Appleton & Lange Publishing Company).

ity in the DNA of the cancers, that is, replication errors. This pattern is also present in the tumors of approximately 15% of persons having "sporadic cancers," suggesting that this abnormality may play a role considerably beyond the classic HNPCC families.[37,42,43] Candidate genes designated *hMSH2* (chromosome 2) and *hMLH1* (chromosome 3) are the human homologues to DNA repair enzymes found in *Escherichia coli* and yeast that are known experimentally to cause a similar pattern of genomic instability.[38,39,44] Thus, although their role in the progression to cancer has not yet been defined, many investigators feel that the discovery of these genes may yield clues to the genetic instability that characterizes colon carcinogenesis, both in familial and in sporadic colon cancers. Knowledge about the possible functions of the other genes involved in colon carcinogenesis is also accumulating. The tumor suppressor gene *P53* appears to be involved in ensuring DNA fidelity by controlling the progression of cells through the cell cycle[45] whereas *APC* and *DCC* gene products may be involved in cell-cell interactions (such as contact inhibition),[46,47] and *ras* may be involved in growth signal transduction.[48] Other such discoveries will undoubtedly be forthcoming from these molecular genetics studies.

TABLE 3.—*Risk of Carcinoma by Adenoma Size, Histologic Type, and Degree of Dysplasia**

Risk Factor	*Patients With Carcinoma, %*
Adenoma size, cm	
<1	1.3
1 to 2	9.5
>2	46.0
Histologic type	
Tubular	4.8
Tubulovillous	22.5
Villous	40.7
Degree of dysplasia	
Mild	5.7
Moderate	18.0
Severe	34.5

*Adapted from Itzkowitz and Kim.[25]

Screening for the Early Detection of Colorectal Cancer

Screening for colorectal cancer is an area of both progress and controversy. The rationale for developing a screening program is clear. Colorectal cancer is a substantial health problem that is potentially preventable in a premalignant stage (given the therapeutic capabilities of fiberoptic endoscopy) or curable in the early stages of malignancy by surgical treatment. The primary prevention of malignancy is not possible because the agents that are responsible for initiating the malignant process have not yet been identified. Therefore, the goal of a colorectal cancer screening program is to improve morbidity and mortality by allowing neoplasms to be identified at a premalignant or potentially curable malignant stage while maintaining patient acceptability and treatment cost-effectiveness. Because screening the entire United States

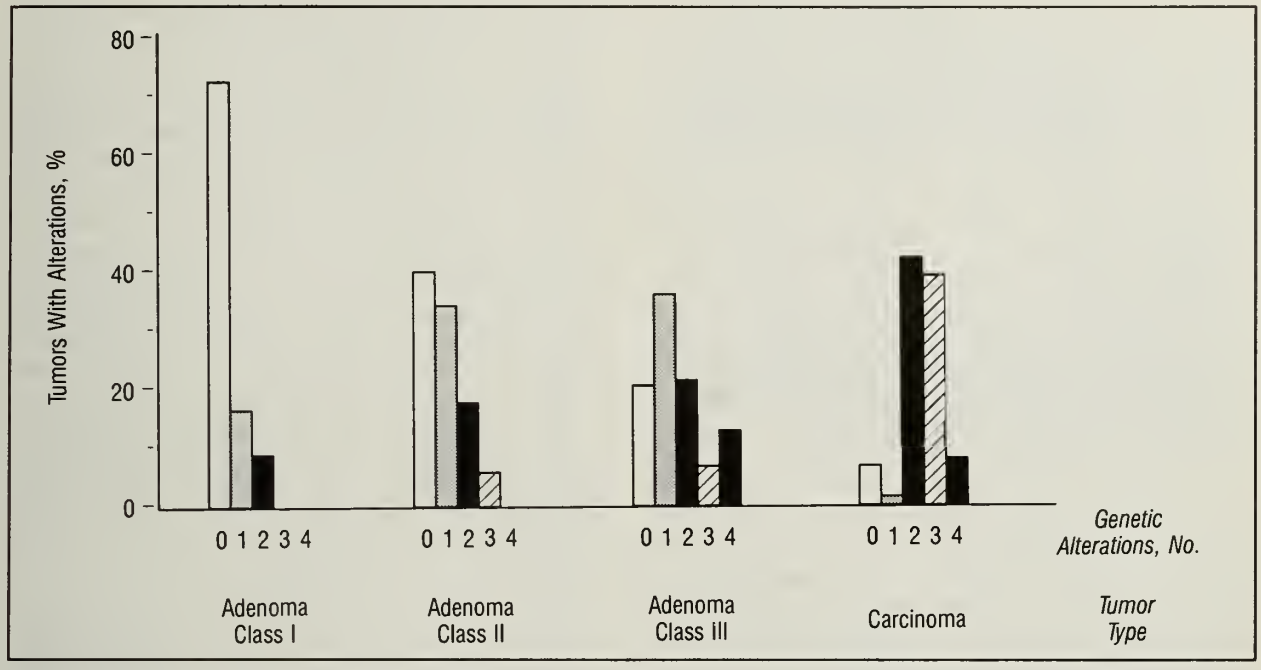

Figure 4.—The accumulation of genetic alterations (*ras* point mutations, 17p/*P53*, 18q/*DCC*, and 5q/*APC* deletions) is shown as a function of position in the adenoma-carcinoma spectrum (adapted from Vogelstein et al[33] with permission from the authors and the Massachusetts Medical Society).

population is not practical, the identification of subgroups at increased risk for colorectal cancer is important.

Table 4 lists some of the risk factors approximately in order of increasing risk of colorectal cancer developing. Age itself is a risk factor.[24] Before age 40, the incidence of colorectal cancer in the general population is less than 1 per 100,000. This incidence then begins to rise and roughly doubles with each decade after age 50, reaching almost 500 per 100,000 by age 80. Having a single first-degree relative with colorectal neoplasm(s)[49] or a history of genitourinary or breast cancer carries a slightly increased risk for colon cancer, perhaps on the order of 1.5- to 2-fold over the general population. Whether this slightly increased risk is due to the inclusion of patients with HNPCC (Lynch II syndrome) or truly represents an increased risk for sporadic adenomas and carcinomas is not clear.

Several conditions are listed as conferring a moderately increased risk for colon cancer. These include Crohn's disease,[50] having two first-degree relatives with colorectal cancer,[16] and having had colorectal cancer.[17] Inflammatory bowel disease, specifically ulcerative colitis, has traditionally been associated with an increased risk for colorectal cancer. More recently, it has been recognized that patients with Crohn's colitis are also at increased risk, although at a longer duration of disease and lower incidence than with ulcerative colitis, perhaps because the proportion of involved colonic mucosa in patients with Crohn's colitis is usually lower than with ulcerative colitis. Epidemiologic studies suggest that patients with two first-degree relatives, although not necessarily meeting the strict criteria for HNPCC (discussed later), may have a fivefold to sixfold higher risk of colon cancer developing than a "normal" population. There is also evidence that the development of so-called sporadic adenomatous polyps has an inherited component.[51] Patients with previous adenomatous polyps are also thought to be at a moderately increased risk if their polyps were multiple, larger than 1 cm, or had an unfavorable cellular pattern—that is, moderate to severe atypia or carcinoma in situ. Surprisingly, a previous colon cancer does not seem to confer a substantially greater risk for colorectal cancer than having a large adenoma or one with an unfavorable histologic type, unless other neoplasms are present at the time of diagnosis.[24]

A number of conditions are associated with a high risk for colon cancer. Ulcerative colitis increases the risk of colorectal cancer, although the magnitude of the risk is not known with certainty. The risk begins to rise seven

TABLE 4.—*Patient Characteristics of Those at Increased Risk (Mild, Moderate, or High) for Colorectal Cancer*

Increased Risk	*Patient Characteristic*
Mild	Age over 40
	First-degree relative with colorectal neoplasm
	History of genitourinary or breast cancer
Moderate	Crohn's disease
	Previous colon cancer
	Previous adenomatous polyps (multiple, large, or high degree of dysplasia)
	2 First-degree relatives with colon cancer
High	Ulcerative colitis (long duration)
	Hereditary nonpolyposis colon cancer
	Familial adenomatous polyposis or Gardner's syndrome

TABLE 5.—*Screening Trials Using Fecal Occult Blood Testing (FOBT)**

Location	Cohort Size, in thousands	Positive FOBT, %	Dukes' Stage A or B Cancer† Screened Group, %	Dukes' Stage A or B Cancer† Control Group, %
Sweden	27	1.9	65	33
England	107	2.1	90	40
New York.....	22	1.7	65	33
Minnesota	48	2.4	78	35
Denmark	62	1.0	81	55

*Data from Vasen et al,[57] Simon,[58] Hardcastle et al,[59] Kewenter et al,[60] Kronborg et al,[61] Winawer et al,[63] Thomas and Hardcastle,[64] Kewenter et al,[65] and Kronborg et al.[66] Adapted from Bresalier and Kim[17] with permission from the authors and WB Saunders Company.

†In each case a higher percentage of possibly curable Dukes' A and B lesions were diagnosed in the screened group than in an unscreened control group (see text).

to ten years after the onset of the disease,[52] with several large studies indicating that the cumulative risk of colon cancer developing is approximately 5%, 15%, and 25% after 20, 30, and 35 years of disease duration, respectively. Several factors such as young age at onset, greater extent or severity of colitis, and the presence of dysplasia on initial surveillance colonoscopy may define subpopulations at increased risk for colorectal cancer.[53-56] Familial adenomatous polyposis and Gardner's syndrome are autosomal dominantly inherited syndromes linked to abnormalities in the *APC* gene in which colon cancer will develop in virtually 100% of affected patients without intervention.

The realization that more colonic neoplasms have a hereditary component than was previously thought has fueled interest in HNPCC (including Lynch syndromes I and II). This hereditary syndrome until recently was defined solely by strict historical criteria:

- Three or more relatives have histologically verified colorectal cancer, one of whom is a first-degree relative of the other two;
- Colorectal cancer involves at least two generations; and
- One or more colorectal cancer cases are diagnosed before age 50.[57]

Using these strict criteria may well underestimate the prevalence of HNPCC, however, because some families with a clear predilection for colon cancer do not meet all of these criteria. The recently described genetic defects on chromosomes 2 and 3 appear to be the abnormality present in most of these kindreds.[37,42] The fact that a substantial number of HNPCC families are not linked to these two genetic loci indicates that this syndrome may be caused by several different genetic abnormalities that may differ in their clinical characteristics and genetic penetrance.

What methods can be used for screening? A careful history can uncover previous polyps or cancer as well as a genetic predisposition. Physical examination is rarely helpful, particularly with the shift of colonic neoplasms toward the right colon. Symptoms are nonspecific and tend to occur late in the course of colorectal cancer. At present no available serum biomarkers have sufficient sensitivity and specificity for use in colorectal cancer screening. Carcinoembryonic antigen levels can be used to monitor recurrences in patients having undergone apparent curative resections for carcinoembryonic antigen-positive colon cancer. Sigmoidoscopy is extremely sensitive and specific to the extent of the examination and has recently been shown to reduce the mortality from cancer of the rectum and distal colon when used as a screening modality. Both colonoscopy and air-contrast barium enema have the advantage of examining the entire colon, but neither procedure is currently recommended for primary screening.

The most common currently used screening method is fecal occult blood testing (FOBT) using guaiac as a colorimetric indicator for pseudoperoxidase activity (hemoglobin possesses such activity) in the stool. Studies indicate that cancers in the right colon result in a daily blood loss of about 9 ml and cancers in the left colon about 2 ml per day. Normal daily gastrointestinal blood loss is less than 2 ml per day. Only polyps larger than 1.5 cm in diameter consistently cause a blood loss of more than 2 ml per day.[58] In theory, it should be possible to identify most patients with colon cancer and some with large polyps by examining the stool for abnormal amounts of blood. In practice, however, dietary factors and noncolonic blood loss into the gastrointestinal tract cause a considerable number of false-positive tests, particularly when the tests are adjusted to detect blood loss near the 2-ml-per-day level. Nonrehydrated guaiac-based FOBTs will give positive results in about 2% of the population (Table 5)[17,59-66] while missing about 40% of colon cancers and 60% of polyps greater than 1 cm in size.[67] Workups for positive FOBTs will yield no disease in about 50% of cases. Immunologic tests (specific for human hemoglobin) could improve the specificity of a positive FOBT, and preliminary results have been somewhat encouraging. Another possible approach to improving the specificity of FOBT might be the use of a two-tiered system of testing.[67] Even small improvements in specificity could have a major influence on cost-effectiveness when one considers screening programs involving millions of people.

Having presented the disadvantages of fecal occult blood testing, we might ask whether screening using FOBT is effective in decreasing mortality from colon cancer. A number of large trials have suggested that a higher percentage of colorectal cancers in the screened population will be discovered in patients with stage A or B cancer than in unscreened controls—that is, in stages where the cancers have a relatively high chance of cure (Table 5). Two recent studies have also indicated that annual FOBT screening decreases the mortality from colorectal cancer by as much as 33%.[68,69] Given these results, arguments opposing the use of FOBT as a screening modality on the basis of a lack of proven efficacy have been weakened. The major criticism remain-

ing is the cost efficiency of such screening. Although such complex analysis is beyond the scope of this discussion, at least one computer analysis of this issue suggested that the cost per year of life saved (using the data compiled by Mandel and associates[68]) compares favorably with the figures for breast cancer screening for women older than 50 years.[70]

Several other screening modalities have been proposed recently. Hydrocolonic sonography has been suggested as a possible alternative or adjunctive method for visualizing the colon.[71] Applying molecular biologic techniques may yield a new generation of screening tests. The polymerase chain reaction can be used to directly detect *ras* oncogene mutations in the DNA from cells shed into the bowel lumen by neoplasms[72] and in combination with other molecular techniques can detect most *APC* mutations without requiring the sequencing of the entire gene.[73] *P53* and *DCC* abnormalities may serve as adjunctive tests for determining the prognosis and therapy after the diagnosis of colon cancer, but they occur late in the progression to cancer.[74,75] Even though none of the currently known genetic abnormalities appear to be useful for general screening purposes, the available technology can be easily adapted for clinical purposes.

At this point, it is probably not useful to discuss specific screening strategies, as there is no clear consensus on what is the optimum method(s), timing, or interval to use. Several observations should be made, however. Perhaps the most important point is that more frequent screening or surveillance is not necessarily better. For example, a recent article showing the efficacy of sigmoidoscopy in decreasing mortality from colorectal cancer also showed that this protective effect extended as long as ten years after the sigmoidoscopy, which is twice the interval recommended by the American Cancer Society.[76] Fecal occult blood testing, if used for screening, should be done annually. The occurrence of a single adenoma in a patient has often been used to justify repeated annual surveillance examinations. Recent studies, however, have indicated that patients with single adenomas smaller than 1 cm do not have a substantially higher risk for subsequent colonic neoplasms when compared with the rest of the population and therefore do not need an intensive surveillance regimen.[77,78] Surveillance is indicated for patients with a history of adenomas that are large, multiple, or have unfavorable histologic features (tubulovillous or villous adenomas or moderate to severe atypia) because these patients appear to be at increased risk of having subsequent adenomas and cancers. The optimum surveillance interval has not yet been determined, but almost certainly need not be more frequent than every three years once the colon has been cleared of polyps and the mucosa has been adequately visualized.[79] More frequent visualization may be indicated in patients with malignant polyps (when a malignant focus has invaded into the muscularis propria), sessile adenomas, or a strong family history.

Summary and Conclusions

A large body of information supports the adenoma-carcinoma hypothesis. These data suggest that for most colorectal carcinomas, the time course for the development of malignancy from previously normal mucosa is about ten years. Removing adenomas decreases the risk of malignancy subsequently developing, and discovering colorectal cancers at earlier stages decreases the mortality. Screening programs are of arguable cost-effectiveness, but they do appear to increase the percentage of colorectal cancers that are discovered in earlier stages as well as decreasing the mortality of colorectal cancer within the screened population. Screening programs should employ 60-cm flexible sigmoidoscopy—this procedure is not appropriate in patients with HNPCC or inflammatory bowel disease, however—with or without the addition of FOBT. The use of FOBT is somewhat controversial because of the marginal sensitivity and specificity of the tests currently available. It is hoped that technologic innovations and molecular biologic discoveries will allow the development of better screening modalities and that epidemiologic studies will result in the identification of factors that lead to primary prevention.

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Conferences and Reviews

Pharmacotherapy for Benign Prostatic Hyperplasia

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Benign prostatic hyperplasia is a benign neoplasm of the prostate seen in men of advancing age. Microscopic evidence of the disorder is seen in about 70% of men by 70 years of age, whereas symptoms requiring some form of surgical intervention occur in 30% of men during their lifetime. Although the exact cause of benign prostatic hyperplasia is not clear, it is well recognized that high levels of intraprostatic androgens are required for the maintenance of prostatic growth. In recent years, extensive surveys of patients undergoing transurethral resection of the prostate reveal an 18% incidence of morbidity that has essentially not changed in the past 30 years. This procedure is also the second highest reimbursed surgical therapy under Medicare. These findings have resulted in an intensive search for alternative therapies for prostatic hyperplasia. An alternative that has now been well defined is the use of α-adrenergic blockers to relax the prostatic urethra. This is based on findings that a major component of benign prostatic hyperplasia symptoms is spasm of the prostatic urethra and bladder neck, which is mediated by the α-adrenergic nerves. A second approach is to block androgens involved in maintaining prostate growth. Several such drugs are now available for clinical use, and we discuss their side effects and use. We also include the newer recommendations on evaluating benign prostatic hyperplasia that are cost-effective yet comprehensive.

(Narayan P, Indudhara R: Pharmacotherapy for benign prostatic hyperplasia. West J Med 1994; 161:495-506)

Benign prostatic hyperplasia (BPH) describes a benign neoplasm of the prostate that develops in aging men. The pathologic process is called "hyperplasia" because there is new growth of cellular elements of the prostate. The first changes of BPH begin around age 35 years and consist of microscopic stromal nodules that occur around the periurethral glands.[1] Acinar hyperplasia then begins around these microscopic nodules. The process takes years, and in mature hyperplastic glands, nodules varying from a few millimeters to a few centimeters may be found. These nodules may be composed predominantly of glandular elements or fibromuscular elements (stroma) or may be mixed.

The incidence of microscopic BPH is fairly constant in several countries, both in western and developing nations. This suggests a lack of variation in genetic, racial, and environmental influences in the cause of BPH. A review of autopsy and clinical data indicates that the incidence of microscopic disease reaches 70% by 70 years of age, while the incidence of palpable enlargement is about half that of microscopic disease.[2] In the United States, it has been estimated that the probability of a 40-year-old man undergoing surgical therapy for symptomatic BPH during his lifetime is 29%.[3] The prevalence of prostatism in an unselected male population has been reported to be 13% for men between the ages of 40 and 49 and 28% for men older than 70.[4]

Etiologic Basis for Pharmacotherapy

The cause of BPH is unclear. Several hypotheses have been proposed based on histologic, hormonal, and age-related changes noted in men with BPH.[5-7] One hypothesis is that the disorder occurs as a result of a reawakening or reinduction of the inherent capacity of urogenital sinus mesenchyme to proliferate and form prostatic tissue. This is based on the following observations:

- The earliest changes of BPH are seen in the periurethral stroma and glands in the region of the verumontanum from which the prostate originally developed; and
- Embryonic and fetal urogenital sinus mesenchyme from both animal models and humans, when placed in an appropriate environment containing androgens, develops into tissue resembling BPH.

Other hypotheses maintain that BPH occurs as a result of changes in relative levels of estrogen and androgens. As men age, their levels of estrogen rise. This is related to both an absolute decrease in the level of testosterone production and an increased conversion of serum testos-

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ABBREVIATIONS USED IN TEXT

AUA = American Urological Association
BPH = benign prostatic hyperplasia
DHT = dihydrotestosterone
FDA = United States Food and Drug Administration
LH-RH = luteinizing hormone-releasing hormone
PSA = prostate-specific antigen
TGF = transforming growth factor [-α, -β_1, -β_3]
TURP = transurethral resection of the prostate

terone to estrogen in the peripheral adipose tissues. Experiments in dogs suggest that estrogen plays a role in inducing stromal hyperplasia. This stromal hyperplasia may trigger acinar hyperplasia. In human BPH, stromal components predominate, and the ratio of stroma to epithelium may be as high as 5:1.[8] Androgens may play a role in initiating but not maintaining BPH. Castration before puberty is known to prevent the development of BPH. Patients with genetic disorders of androgen function also have poor prostatic growth. But castration in patients with established BPH does not uniformly result in prostatic atrophy.[5-7] The androgen critical to prostatic growth is dihydrotestosterone (DHT). Prostatic tissue DHT levels are found to be similar in men with both normal and hyperplastic glands.[9]

Growth Factors and Benign Prostatic Hyperplasia

The in vivo mitogenic action of androgens may be mediated not only through androgens but also through other hormones or growth factors. The proliferation of prostatic epithelial cells in culture requires glucocorticoid, insulin, epidermal growth factor, prolactin, and other pituitary factors, but not androgens.[10]

Epidermal growth factor and its closely related factor, transforming growth factor (TGF)-α, are synthesized by prostatic epithelial cells in culture and are mitogenic to these cells. Increased expression of epidermal growth factor receptors has been observed in prostatic tissues obtained from men with BPH.[11] Also, an increased expression of transforming growth factor-β (TGF-β_1 and TGF-β_3) has been observed in prostatic tissues obtained from men with BPH.[12] Basic fibroblast growth factor is known to produce glandular hyperplasia of the prostate in mice.[13] Although the functional relevance of these in vitro studies is still unclear, there is a possibility of the overproduction or overexpression of these growth factors in the pathogenesis of BPH. It may be theorized that interaction among epidermal growth factor, transforming growth factors, and fibroblast growth factor could lead to different effects on the epithelium and stroma that in turn lead to nodular prostatic hyperplasia. Strategies aimed at blocking this growth factor pathway may be of therapeutic importance in the future.

Neuroendocrine Differentiation and Benign Prostatic Hyperplasia

The neuroendocrine cells or endocrine-paracrine cells of the body are diffusely situated in the respiratory and gastrointestinal systems and in the pancreatic islets. They have been designated to belong to the APUD (amine precursor uptake decarboxylase) system. Endocrine-paracrine cells are present in relatively large numbers in the prostate and urethra. They are recognized by specific immunohistochemical staining for various secretory products such as calcitonin, bombesin, and serotonin. Most BPH nodules show a pronounced decrease of serotonin immunoreactive cells when compared with adjacent normal prostatic cells. The proliferating and immature nodules, however, show higher positivity for immunoreactive staining. It has been postulated that the proliferating cells are under some type of control (paracrine) by endocrine-paracrine cells.[14]

Pathophysiology of Symptoms

The prostate gland is located immediately below the base of the urinary bladder and completely envelops the urethra. The prostate comprises five regions (zones) that have unique morphologic properties (Figure 1). Benign prostatic hyperplasia develops in the transition zone, which is adjacent to the urethra. The benign enlargement of the transition zone is called prostatic adenoma.

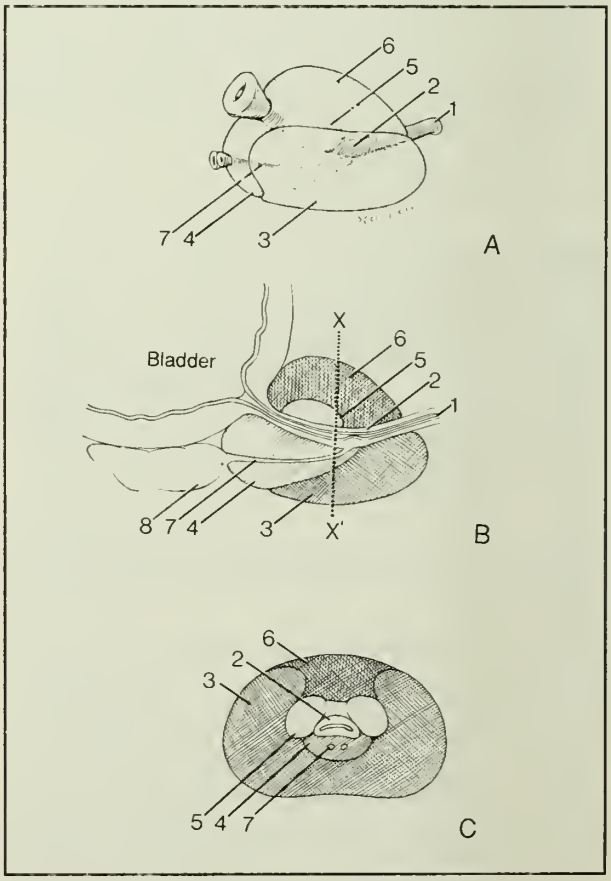

Figure 1.—The schematic represents the various zones of the prostate: A, panoramic view; B, sagittal view; C, transverse section taken at the X-X' of B. The numbers represent the urethra (1), urethral muscle (2), peripheral zone (3), central zone (4), transition zone (5), anterior zone (6), ejaculatory duct (7), and seminal vesicle (8).

TABLE 1.—*International Prostate Symptom Score (IPSS) Questionnaire*

Question	*Not at all*	*Less than 1 time in 5*	*Less than half the time*	*About half the time*	*More than half the time*	*Almost always*
Incomplete emptying: Over the past month, how often have you had the sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
Frequency: Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
Intermittency: Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
Urgency: Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
Weak Stream: Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
Straining: Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
Nocturia: Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5
					Total IPSS Score =	

Question	*Delighted*	*Pleased*	*Mostly satisfied*	*Mixed; about equally dissatisfied and satisfied*	*Mostly dissatisfied*	*Unhappy*	*Terrible*
Quality of Life Due to Urinary Symptoms: If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Enlargement of the prostate may compress the urethra and block the free egress of urine during micturition. The clinical manifestations of BPH are related primarily to obstruction caused by prostatic enlargement. The symptom complex associated with BPH is called prostatism. Prostatism is composed of obstructive and irritative symptoms, although these terms are not mutually exclusive. The obstructive symptoms include hesitancy and straining to initiate urination, a diminished caliber and interrupted urinary stream, and postmicturition dribbling. The irritative symptoms include urinary frequency and nocturia (awakening during the night to urinate), dysuria (burning during urination), and urgency (the impending need to urinate). The symptoms of frequency and nocturia, however, may also be due to a high amount of residual urine and a manifestation of prolonged obstruction. Initially the bladder effectively compensates for the obstruction by increasing bladder muscle mass (hypertrophy). As the severity of the obstruction progresses, bladder hypertrophy is unable to compensate for the obstruction, resulting in incomplete bladder emptying. Incomplete bladder emptying exacerbates the symptoms of prostatism and predisposes to urinary tract infection and recurrent hematuria. The most severe sequelae of bladder outlet obstruction due to BPH are complete urinary retention, bladder diverticula, bladder calculi, urinary infection, hydronephrosis, and chronic renal insufficiency.

Patients with BPH may also have symptoms not directly related to the urinary tract. These include hernias, hemorrhoids, change in bowel habits, and other manifestations of increased abdominal pressure and straining during voiding.

Traditionally a number of methods have been used to assess BPH symptoms objectively. These include the Boyarsky symptoms score, Madsen and Iversen symptoms score, and others. Recently a more patient-friendly symptom index for BPH was developed and validated by a multidisciplinary measurement committee of the American Urological Association (AUA).[15] This symptom index includes seven questions covering frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency. A modification of this, called the international prostate symptom score, which includes a question concerning the quality of life due to urologic symptoms (Table 1), has been adopted by the World Health Organization for use internationally. This should allow the standardization of nomenclature and a comparison of future studies among various countries.

Mechanisms of Obstruction and Rationale for Pharmacotherapy

Current pharmacotherapy for BPH is based on agents that relax the smooth muscles of prostatic urethra and stroma and those that deprive acinar cells of androgen.

TABLE 2.—*Drugs That Have Been Tried in the Medical Management of Benign Prostatic Hyperplasia**†

Drug Class	*Drug (Code Designation)*	*Trade Name*
α_1-Adrenergic antagonists	Prazosin HCl	Minipress
	Terazosin HCl	Hytrin
	Doxazosin mesylate	Cardura
	Phentolamine mesylate	
	YM-617	
	Nicergoline	
	Indoramin	
	Ketanserin	
	Yohimbine HCl	
Antiandrogens		
Selective		
5α-Reductase inhibitors	Finasteride	Proscar
	Epristeride (SK&F 105657)	
Agents blocking androgen uptake and causing receptor blockade	Flutamide	Eulexin
	Cyproterone acetate	
	Nilutamide	
	Oxendolone	Prostetin
	Gestonorone caproate	Depostat
	Casodex (ICI 176,334)	
Nonselective		
Gn-RH analogues	Nafarelin acetate	Synarel
	Leuprolide acetate	Lupron
	Goserelin acetate	Zoladex
Estrogens	Diethylstilbestrol	
	Chlorotrianisene	TACE
Progestational agents	Megestrol acetate	Megace
	Hydroxyprogesterone acetate	Primostat
	Hydroxyprogesterone caproate	
	Medrogestone	
Aromatase inhibitors	Testolactone	Teslac
	Atamestane	
Steroidogenesis inhibitors	Aminoglutethimide	
	Ketoconazole	
Prolactin inhibitor	Bromocriptine mesylate	
Miscellaneous agents	Candicidin	
	Sitogluside (WA 184)	
	Probucol	
	Cimetidine	Tagamet
	Physosterols	
	Extract of the plant *Serenoa repens*	Permixon
	Spironolactone	
	Tamoxifen citrate	
	Bazoton	
	Fluorouracil	

Gn-RH = gonadotropin-releasing hormone, HCl = hydrochloride

*The list is not exhaustive.
†Some agents act by more than one mechanism.

Various agents have been tried in the treatment of BPH (Table 2).* They may be broadly grouped into those affecting the dynamic component of urethral obstruction, namely the smooth muscle and prostatic stroma, and those affecting the glandular elements by androgen deprivation. The mechanism of action of many agents claimed to be useful in BPH is not clearly understood.

Caine has suggested that obstruction due to BPH occurs because of two factors[16,17]: a dynamic component is thought to occur as a result of the contraction of smooth muscles of the prostate and prostatic urethra and is mediated mostly by adrenergic receptors; and a mechanical component of obstruction is related to the presence of a mass of hyperplastic acinar or stromal tissue that compresses and narrows the urethral lumen. There is some evidence that the presence and density of stromal content in BPH may relate to the severity of obstruction.[18]

*See also the editorial by A.V. Smith, MD, "Pharmacologic Management of Benign Prostatic Hyperplasia—Changing Times" on pages 521-523 of this issue.

TABLE 3.—*Natural History of Benign Prostatic Hyperplasia*

Study	Patients, No.	Follow-up, years	Prospective or Retrospective	Criterio for Study Entry ond Follow-up	Improvement, %	Stobilizotion, %	Progression, %
Clarke et al, 1937[26]	36	3-4	Retrospective	Not defined	69	17	15
Birkhoff et al, 1976[27]	26	>3	Retrospective	Not defined	27	15	58
Ball et al, 1981[28]	107	5	Retrospective	Not defined	29	47	24
Barnes and Marsh, 1983[29]	208	2.4-4.8	Prospective	Not defined	62	9	29
Total	377	4.2			46.75	27	31.5

Current understanding of the biologic mechanisms of obstruction is limited and does not extend to two common clinical facts. The first is that the size of the prostate does not always correlate with the severity of symptoms or objective signs of obstruction. The second is the discrepancy between the histologic changes of BPH and the presence and severity of symptoms. From a physiologic standpoint, five conditions in patients with symptoms of "BPH" may exist singly or in combination.[19] These are prostatic urethral obstruction, impaired detrusor contractility, detrusor instability, sensory urgency, and primary vesical neck obstruction. All these conditions likely result from varying combinations of prostatic enlargement and subtle neurologic dysfunction, all due to age-related central nervous system degeneration. Alternatively, a hyperplastic prostate during growth may disrupt normal sphincteric function. Thus, it is not surprising that prostatectomy fails to relieve symptoms of prostatism in about 20% of patients because the symptoms may be caused by poorly understood deficits in neurosensory pathways regulating micturition and sphincteric function.

Transurethral prostatectomy is the most common surgical procedure currently performed for the treatment of BPH.[20] Outcome analyses have questioned the results of transurethral resection of the prostate (TURP). Patients undergoing TURP have been reported to be at greater risk from cardiovascular death than patients undergoing open prostatectomy.[21] Recently these findings were disputed,[22] and it was reported that transurethral resection for BPH does not increase long-term mortality and that comorbid illnesses and older age probably account for the apparent increase in long-term mortality after TURP. The morbidity of the procedure remains unchanged, however. In a review in 1962, the morbidity after TURP was reported to be 18% and the mortality 2.5%.[23] More recently, the AUA cooperative study of 3,885 patients after the procedure revealed an overall complication rate of 18% and 0.2% mortality.[24] Thus, the search for alternative therapies has been prompted by patients' preferences for less invasive forms of treatment without prohibitive side effects. Apart from pharmacotherapy, other methods undergoing trials for the treatment of BPH include laser ablation, microwave hyperthermia, and prostatic stents. Ultimately, the role of surgical treatment and newer modalities must be based on relative effectiveness, cost, morbidity, effect on quality of life, expectations, and treatment preferences of patients.

Natural History of Benign Prostatic Hyperplasia and Implications for Medical Therapy

A knowledge of the natural history of BPH is useful to plan therapeutic interventions and assess efficacy and outcome over time. The four reported studies on the natural history of BPH are summarized in Table 3.[25-29]

All four studies have major flaws. Only one study is prospective. They all involve small numbers of patients, and follow-up is less than five years in three of the four studies. In addition, criteria for study entry and follow-up criteria to study natural history are ill defined. All of these studies, however, have common features that suggest that progression in BPH is variable, certainly not inevitable, and perhaps to some degree reversible. Based on these limited data, medical intervention may postpone surgical intervention in some patients and avoid it in others. This possibility is supported by our own experience with 900 patients on medical therapy over six years. Among patients who have undergone medical therapy for six months or more, surgical therapy has been required in less than 15% of patients. This may change with further long-term follow-up, however. Another possible reason for a lower rate of surgical intervention in patients on medical therapy may be that most of these patients, though clearly symptomatic, are motivated to receive medical therapy and are younger than those undergoing TURP.

Mechanism of α-Blocker Therapy

Catecholamines mediate a variety of physiologic and metabolic responses in human beings as a result of their interactions with receptors located on the plasma membrane. The adrenergic receptors are classified as α_1, α_2, and β receptors.[30] In general, α-adrenergic receptors mediate vasoconstriction, intestinal relaxation, and pupillary dilation. α_1-Adrenoceptors are generally located postsynaptically on the vascular smooth muscle and mediate smooth muscle contraction. Each of the three major adrenoceptors has been further subdivided into three subtypes. Pharmacologically, α_1-adrenoceptors have been further subtyped into α_{1A} and α_{1B} based on studies using phentolamine and chloroethylclonidine. Both these subtypes have been characterized by using molecular cloning techniques; in addition, a further subtype, α_{1C}, which was not identified by pharmacologic methods, has been recognized using molecular cloning methods.[31] Lepor and associates used functional and radioligand binding assays to identify α_{1A} and α_{1B} subtypes in the human prostate.[32]

These studies suggested that the dominant α_1 subtype in the human prostate is α_{1A}. More recently, by molecular techniques, the presence of the α_{1C} subtype in the human prostate was reported.[33] Quantitative solution hybridization assays showed that the α_{1C} subtype constitutes 70% of the total α_1-adrenoceptors in the human prostate. Furthermore, in situ hybridization localized the α_{1C}-adrenoceptor messenger RNA predominantly to the stromal component.

Understanding of the presence of multiple α_1-adrenoceptor subtypes in the human prostate and their implications in pharmacotherapy is still evolving. Changes in the level of receptor subtype expression may be involved in either the development or progression of a disease state. The heterogeneity of α_1-adrenoceptor distribution may also explain the variable response to pharmacologic agents. Further studies may facilitate the development of more uroselective or prostate-specific α-blockers than are currently available and with fewer side effects.

The rationale for using α-blockers in the treatment of BPH was based on the observation that the contractile properties of prostate smooth muscle are mediated by α_1-adrenoceptors.[16,17] It has been shown that the stromal:epithelial ratio in normal prostates is 2:1, and in BPH it is 5:1.[8,18] Stromal tissue is therefore an important component of BPH. This stroma may be composed of varying amounts of smooth muscle and fibrous connective tissue. In addition, the prostatic urethra and bladder neck have a substantial amount of smooth muscle that comes into play in causing symptoms of BPH. Biologic and functional studies of lower genitourinary tract tissues have shown that adrenoceptors are sparse in the bladder but predominate in the bladder neck and prostate (Figure 2). α_1-Adrenergic antagonists are therefore ideally suited for the treatment of the dynamic component of bladder outlet obstruction because they can selectively reduce resistance along the bladder outlet without impairing detrusor contractility. The mechanism of action of α_1-blockers is shown in Figure 3. The difference between a selective and nonselective α-blocker (such as phenoxybenzamine) is that nonselective blockers also prevent the reuptake of norepinephrine into the adrenergic nerve ending. Although nonselective α-blockers theoretically cause a more complete blockade, their increased side effects preclude long-term use in clinical practice.

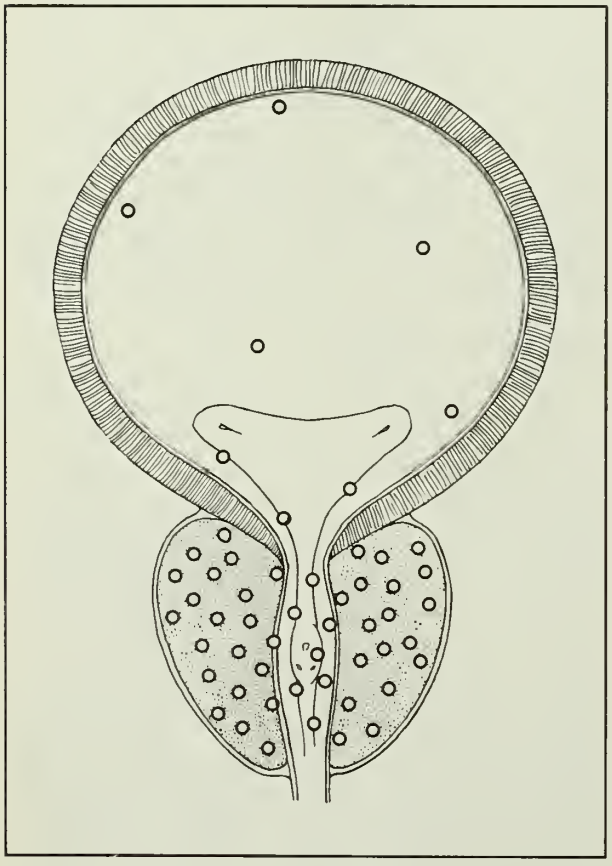

Figure 2.—The schematic representation shows α-adrenergic receptor distribution in the prostate, urethra, and bladder.

Results of α-Blocker Therapy

In 1976 the α-blocker phenoxybenzamine was reported to be effective for the treatment of BPH.[16] Over the past 15 years, more than 30 clinical trials evaluating α-blockers for the treatment of BPH have been reported. Most of these studies were deficient in their protocol design, and the criteria for enrollment, assessment of efficacy, and statistical analysis were not standardized. The α-blockers evaluated for BPH have included phenoxybenzamine, nicergoline, thymoxamine (moxisylyte), prazosin, alfuzosin, terazosin, doxazosin, and YM-617. Despite various protocol deficiencies, the improvements in urinary flow rates have been consistent. Overall, urinary flow rates improve about 50% following the administration of α-blockers (Table 4). The degree of symptomatic improvement following α-blockade is difficult to ascertain because quantitative symptom score questionnaires have rarely been used to measure efficacy. The toxicity associated with the various α-blockers was variable. But the incidence and severity of adverse reactions associated with the nonselective α-blockers, such as phenoxybenzamine, were always greater than the toxicity of selective α-blockers such as prazosin and terazosin.[34,35]

Terazosin is one of two selective, long-acting α_1-adrenoceptor antagonists that are currently approved by the United States Food and Drug Administration (FDA) for the treatment of hypertension. Its longer half-life allows for a once-a-day dosage regimen. The US experience evaluating the safety and efficacy of terazosin was recently evaluated in 313 men with symptomatic BPH.[36] The total Boyarsky symptoms score decreased 43% and 21%, respectively, in the groups treated with 10 mg a day and with placebo, and peak urinary flows increased 37% and 12%, respectively. The adverse events were relatively minor and easily reversed. Beneficial results with the use of terazosin at dosages as high as 10 mg per day have also been reported by others.[37-39] The overall reduction in symptoms ranged from 57% to 68%, and 32% improve-

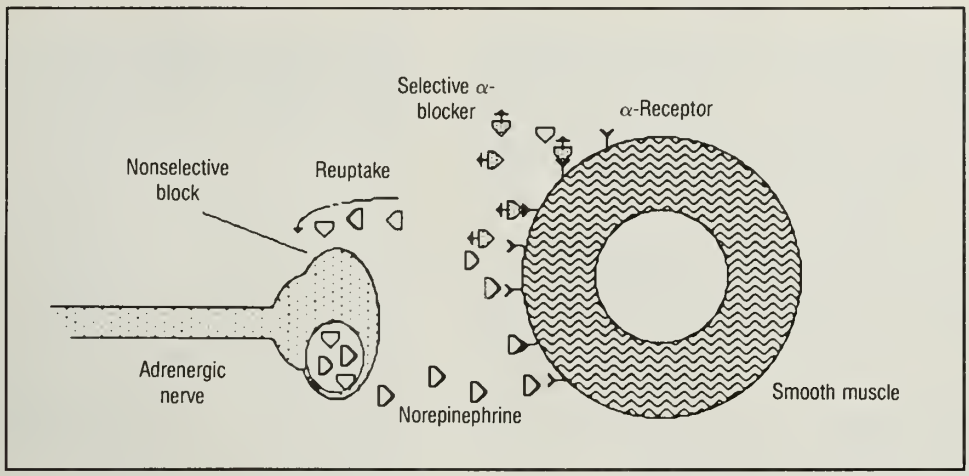

Figure 3.—The mechanism of action of α-adrenergic blocking agents is shown.

ment was observed in urinary flow rates. No major adverse effects, including orthostatic hypotension, were seen in any with the relatively high doses of terazosin.

Alfuzosin is another long-acting, selective α_1-blocker that has been found beneficial in the treatment of BPH. In a report of a multicenter, randomized, placebo-controlled trial,[40] alfuzosin at a daily dose of 7.5 to10 mg produced good to very good improvement in symptoms in 61% of patients; however, there were no significant differences in peak urinary flow rates between the alfuzosin-treated and the placebo-treated groups. The incidence of side effects such as hypotension, dizziness, asthenia, and impotence was similar in both groups. In a French BPH study of alfuzosin, 7,093 patients were enrolled in an open-label, nonrandomized, and prospective manner. The preliminary results of this study have confirmed the effectiveness of alfuzosin in diminishing symptoms of BPH in placebo-controlled studies.[41] The irritative symptom score improved by 57% and the obstructive score by 40%. Results of the 6- and 12-month evaluations are awaited.

Additional Beneficial Effects of α-Blockers

The possible clinical efficacy of α-blockers for the aging male population is not limited to treating infravesical obstruction from BPH. In older men, the prevalence of coexisting hypertension, hypercholesterolemia, and BPH is high. Because terazosin is an effective antihypertensive agent and has the ability to reduce total cholesterol and triglyceride levels substantially, its use in older men with BPH is especially appropriate.[42]

Adverse Events

Overall, the incidence of adverse events from the use of α-blockers ranges from 7% to 10%.[36] In a summary review of US trials,[36] although higher frequencies of asthenia, flu syndrome, and dizziness were observed in the groups treated with terazosin, the differences from the group given placebo were not significant when tested by Fisher's exact test. There was a significantly greater incidence of postural hypotension in the group treated with 5 mg of terazosin than in the placebo-treated group. Syncope developed in only one patient (of 79; 1.3%) in the group treated with 10 mg. The incidence of syncope for all terazosin-treated patients was less than 0.5%.

Combination of Androgen Suppression and α-Blockade

Although several investigators have alluded to the possible role of combination pharmacotherapy (androgen suppression and α-blockers), there is little published information on BPH. The mechanisms of action of α-blockade and androgen suppression for relieving infravesical obstruction in BPH are different. The minimal and nonoverlapping toxicity associated with terazosin and finasteride monotherapy has prompted a large-scale, four-arm Department of Veterans Affairs cooperative trial (currently in progress) to test the combination of these agents.

Timing and Indications for Pharmacotherapy

Because BPH is not invariably progressive, the timing of intervention for each patient varies and depends on the severity of symptoms and the presence of complications. Patients with mild symptoms need no therapy other than watchful waiting and a periodic check of serum creatinine levels and urinalyses. α-Blocker therapy is recommended for all other patients with moderate and severe symptoms of BPH, but not those in retention or with complications (such as hydronephrosis, recurrent hematuria, or stones).

TABLE 4.—*Outcome of α-Blockade for Benign Prostatic Hyperplasia—Summary of Studies*

α-Blockers	*Patients, No.*	*Efficacy Measurements*	
		Urinary Flow Improved, %	*Total Symptoms Score Improved, %*
Nonselective	294	44	NA
Selective	350	49	NA
Selective long-acting	565	54	47

NA = not assessable

The size of the prostate does not exclude the use of pharmacotherapy. Pharmacotherapy is also recommended for patients unable, unfit, or not desirous of surgical therapy, as initial therapy, especially in younger patients (45 to 55 years), as a temporizing measure before later surgical intervention, and as an additional measure during initial recovery after surgical or laser therapy.

Evaluation of Benign Prostatic Hyperplasia

The Agency for Health Care Policy and Research is preparing guidelines for choosing tests for the evaluation of BPH. Until these are published, the following tests are suggested:

- A history and physical examination, including medication history;
- An AUA symptom score evaluation;
- Abdominal, genital, and digital rectal examinations;
- A urinalysis;
- A serum creatinine level;
- A uroflow study; and
- A residual urine determination.

The single most important criterion for therapy is the symptom score. The AUA symptom score questionnaire has been validated and is designed to be answered by patients. It comprises seven questions, each of which can have a score of 0 to 5. The maximum score therefore is 35. For scores below about 10, watchful waiting is recommended in the absence of complications. Therapy is indicated for those patients with moderate (scores of 10 to 20) or severe obstruction (scores of > 20). In the absence of hematuria or an abnormal serum creatinine value, an upper tract study has no clinical consequence and is not cost-effective. Residual urine measurements are required by Medicare in many states. Residual urine, although not an independent prognostic indicator, may help in patient counseling regarding voiding patterns after therapy and, if very high (> 300 ml), may help decision making regarding the need for surgical therapy. The need for measuring prostate-specific antigen (PSA) levels in patients with BPH is also unresolved; we obtain PSA measurements in all men aged 50 to 70 years, and 70% of urologists do the same, as noted in a recent survey.[43]

Use of α-Blockers in an Office Practice

In our practice, we recommend giving terazosin hydrochloride (Hytrin, Abbott Laboratories), 1 mg at night, with a check of blood pressure the next morning for three consecutive nights. If there is no change in blood pressure or the change is minimal—less than 5 to 10 mm of mercury—the patient self-titrates the dose after two to three days to 2 mg and continues taking 2 mg for two weeks. The blood pressure is again checked, and if there are no side effects, the patient may increase the dose to 5 mg. We see him at six weeks and evaluate the blood pressure, the AUA symptom score, and urinary flow. Depending on the relief of symptoms and side effects, patients may opt to continue taking 2 mg, 5 mg, or increase to 10 mg. Most patients prefer α-blockers at 2- to 5-mg doses. About 15% of patients titrate up to a 10-mg dose. There is incremental response in symptom relief and urinary flow with as high as 10 and even 20 mg of terazosin. Side effects are occasionally seen to worsen after 5-mg doses.

Differences Between Various α-Blockers

Nonselective α-blockers are more potent than selective α-blockers because of their double action of blocking neurotransmitters both at the smooth muscle level and in the reuptake at the adrenergic nerve ending. But they have more side effects, and agents such as phenoxybenzamine are not recommended for long-term use as they have been shown to cause sarcomas in rodents. The main difference among others is in the duration of action (Table 5); also, we have found the first-dose side effect of terazosin to be less than that of prazosin. Prazosin is less expensive than terazosin. To date, however, only terazosin has undergone extensive testing for the treatment of BPH, and it is the only α-blocker that has FDA approval for use in treating BPH.[44,45]

Duration of Therapy

Although symptoms diminish after two to three days of α-blocker therapy, response is incremental for as long as six months, at which time patients reach a plateau.[46] α-Blocker therapy is therefore recommended for a minimum of six months to a year to get maximal response. Because the available natural history data of BPH indicate periods of progression with intervals of stability, pharmacotherapy can be used intermittently. It is recommended that patients titrate doses of α-blockade down if they want to attempt discontinuing medications.

Role of α-Blockers and Pharmacotherapy in Relation to Other Available Therapies

α-Blockers are recommended as first-line therapy in most patients requiring medical therapy because of their relative efficacy, rapid onset of action (one to three days), and relatively low cost. α-Blockers cost $0.50 to $1 per day (finasteride costs $1.75 per day); if patients are already taking antihypertensive medications, the cost savings are greater because two diseases can be treated with one agent. Urologists should preferably work with an internist or cardiologist to adjust doses of α-blockers or switch therapies with other antihypertensive agents as feasible. The major advantage of finasteride is in its low side-effect profile—allowing its use in patients taking several cardiac medications—and its possible superior efficacy in patients with predominantly acinar hyperplasia. For patients who prefer finasteride as first-line therapy, we recommend α-blockers for the first three months before finasteride efficacy has begun.

Drugs Affecting the Hormonal Control of Prostate

Several possible levels in the hypothalamus-pituitary-gonadal-prostate axis can be blocked to influence

TABLE 5.—*Pharmacologic Agents in Benign Prostatic Hyperplasia*

Agent	*Mechanism of Action*	*Dose Schedule, mg/day*
Phenoxybenzamine	α_1- and α_2-Blockade	5 to 10 × 3 orally
Prazosin	α_1-Blockade	1 to 5 × 2 orally
Terazosin	α_1-Blockade	1 to 10 × 1 orally
Indoramine	α_1-Blockade	50 × 2 orally
Alfuzosin	α_1-Blockade	3 to 4 × 3
Nicergoline	α_1-Blockade	4 × 2 IM
YM-617	α_1-Blockade	0.2 to 0.8 × 1 or 2 orally
Ketanserin	Serotonin antagonist; possible α-blockade	10 × 1 orally

IM = intramuscularly

prostatic growth (Figure 4). Nearly a century ago, bilateral orchiectomy was reported to be beneficial in the treatment of BPH.[47] More recently, in 1986, the beneficial results of bilateral orchiectomy were reported in five patients with BPH with chronic urinary retention.[48] Because surgical orchiectomy is irreversible, is not liked by patients, and produces variable results, it has never gained popularity as a treatment option for BPH. Luteinizing hormone-releasing hormone (LH-RH) analogues such as leuprolide, buserelin, and nafarelin produce reversible "medical castration" by suppressing pituitary gonadotropin secretion. After about four weeks of taking an LH-RH analogue, a patient's serum testosterone concentration reaches castration levels (<50 μg per dl). Several published articles on the use of LH-RH analogues for BPH have reported their beneficial effect in a few selected patients who were unsuitable for any operative intervention.[49-51] Almost all patients had loss of libido, impotence, and hot flushes. Despite good urologic results, the universal occurrence of these side effects, cost, and their lack of effect on adrenal androgens (which could theoretically contribute to prostatic growth) make LH-RH analogues unlikely to be used routinely in patients with BPH.

Traditionally, estrogens and progestational agents have been tried in the treatment of BPH.[52] Because of the generalized androgen suppression produced by these agents, their administration is associated with a number of undesirable side effects such as loss of libido, impotence, and gynecomastia. Their effects on urinary function are also variable. Attempts have been made to achieve selective blockade of androgen action at the cellular level in the prostate. One such method is the use of 5α-reductase inhibitors, the enzyme required for intraprostatic conversion of testosterone to its active form, dihydrotestosterone (DHT). It has been observed that patients with the rare condition of genetically inherited 5α-reductase deficiency have low levels of DHT. They have a small prostate gland throughout life, and BPH does not develop (Merck & Company, Inc, Whitehouse Station, NJ, product insert for Proscar, 1992). This was the basis for the development of the drug finasteride for the medical treatment of BPH.

Finasteride

Finasteride (Proscar) is a competitive, specific inhibitor of 5α-reductase enzyme (Figure 4).[53] After a single 5-mg oral dose, it produces a rapid reduction in serum DHT concentration within 8 hours of administration, and this is maintained for as long as 24 hours. It does not affect the hypothalamus-pituitary-testicular axis as evidenced by a normal response of luteinizing hormone and follicle-stimulating hormone to gonadotropin-releasing hormone. It is available as 5-mg tablets for oral administration. In a large, multicenter, double-blind study on the effect of finasteride in men with BPH,[54] it was noted that serum DHT concentrations decreased to castration levels soon after finasteride therapy was initiated. Serum testosterone and luteinizing hormone concentrations increased only slightly. A median reduction in prostate volume of 19% was noted within three months of the initiation of therapy. This was associated with a substantial decrease in serum PSA levels, thus indicating a decrease in prostatic epithelial cell function. There was a significant decrease in symptoms of obstruction and an increase in maximum urinary flow rates (by 22%). There were no major side effects, but a higher incidence (5%) of decreased libido and decreased ejaculatory volume occurred in men receiving finasteride.

In another trial of 67 men using 10 mg of finasteride per day for one year, peak flow rates increased by a mean of 4 ml per second with a 3-ml-per-second improvement in 70% of patients.[55] The worldwide long-term multicenter trial on the use of finasteride for BPH is now in year 3, and both symptom reduction and urinary flow improvement have been maintained. In fact, at year 3 there is further reduction in the symptom score and improvement in urinary flow compared with the end of year 1. In summary, finasteride reduces symptoms objectively and subjectively in 30% to 40% of patients on therapy, and it has an excellent safety profile. The cost of the drug is about $1.75 per day.

In current practice, finasteride is recommended in a dose of 5 mg per day. Spouses who are of childbearing age are advised not to come in contact with the semen of men who are taking finasteride, to avoid any effects on a developing fetus. Side effects of finasteride include decreased libido (4.7%), ejaculatory disorder (4.4%), and impotence (3.4%). Finasteride interacts little with other medications and may be safely used in patients taking α-blockers, β-blockers, theophylline, digoxin, sodium warfarin, diuretics, anti-inflammatory agents, calcium channel blockers, and histamine-2 antagonists. No dose reduction is necessary for renal failure, although patients with liver dysfunction should be monitored because finasteride is metabolized by the liver. About 40% of metabolized finasteride is excreted in urine and 59% in stool. There is no interaction with food. The long-term risks of therapy with 5α-reductase inhibitors are not known.

In clinical trials, patients taking finasteride have a decrease in PSA levels of 41% at six months and 48% at 12 months. Although there is a new lower baseline level, finasteride does not appear to change the ability of PSA

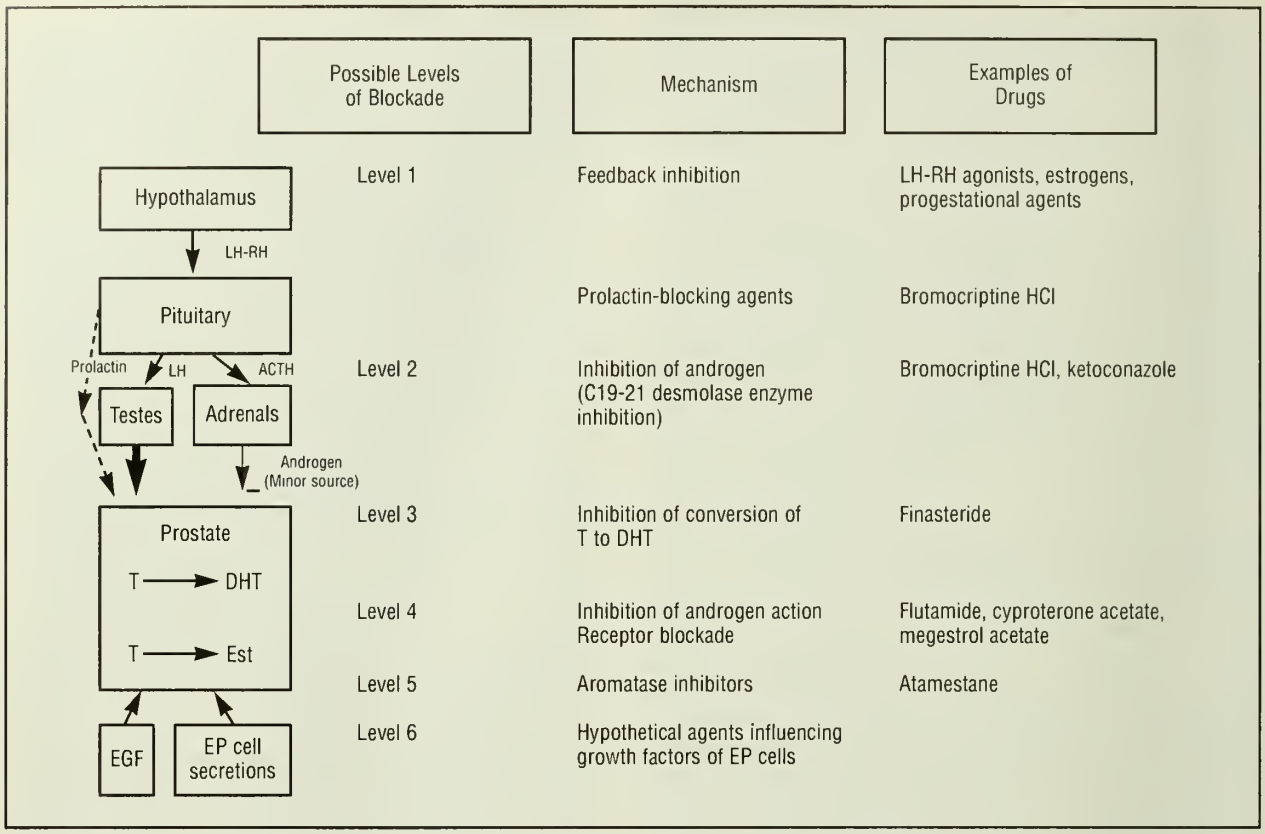

Figure 4.—The diagram shows the hypothalamus-pituitary-testicular-prostate axis and possible levels of its blockade. Note: Some agents may have more than 1 mechanism of action. ACTH = adrenocorticotropic hormone, DHT = dihydroxytestosterone, EGF = epidermal growth factor, EP = endocrine-paracrine, Est = estrogen, HCl = hydrochloride, LH = luteinizing hormone, LH-RH = LH-releasing hormone, T = testosterone

levels to rise with the development of cancer. In the multicenter trial, most patients on finasteride therapy in whom cancer developed had elevated PSA levels before therapy, and while on therapy, PSA levels increased concurrently with the development of cancer.[54] The effects of finasteride on PSA need further evaluation.

Epristeride

Epristeride (code designation SK&F 105657), a new chemical compound developed by SmithKline Beecham Pharmaceuticals, is a potent and selective inhibitor of 5α-reductase. It has been shown to reduce serum and prostatic DHT concentrations while maintaining the testosterone levels (P. Audet, D. Jorkasky, B. Ilson, et al: "An Open-Label Study to Examine the Safety, Pharmacokinetics and Pharmacodynamics of SK&F 105657 Administered Orally Daily for Eight Doses in Healthy Elderly Male Subjects," SmithKline Beecham Report No. MP/004/SK&F-105657, 1991). Currently, clinical studies are being done concerning its efficacy in the medical management of BPH.

Flutamide

Another approach to blocking androgen uptake by prostatic cells is to prevent androgen binding to nuclear androgen receptors, the normal mechanism by which androgens are used by prostatic cells. Agents such as flutamide and nilutamide (anandron) act in this manner. Flutamide (Eulexin) is a nonsteroidal antiandrogen with estrogenic, progestational, or antigonadotropic effects. In patients with BPH, trials have shown both objective increases in flow rates and subjective lessening of symptoms. Flutamide also does not lower peripheral serum testosterone levels and therefore is not generally associated with a loss of libido, impotence, or hot flushes. A decrease in libido is noted, however, in 10% to 15% of patients on long-term therapy. Other side effects include diarrhea in 15% and gynecomastia in 30% of patients. Flutamide is also metabolized in the liver, and liver enzyme values increase with continued use. A major disadvantage is cost, which is three times higher than for finasteride.

Other Antiandrogen Agents

There are also antiandrogens that block both luteinizing hormone and nuclear androgen uptake. Among these are cyproterone acetate and megestrol acetate. Cyproterone acetate is a synthetic antiandrogen with progestational activities. This agent inhibits both androgen uptake by androgen receptors and the release of gonadotropins from the pituitary. In patients with BPH, it has improved flow rates and lessened voiding symptoms.[56] Megestrol acetate is another progestational antiandrogen that blocks

TABLE 6.—*Antiandrogen Mechanisms of Action and Side Effects*

Class of Drug	*Agents (Code Designation)*	*Mechanisms of Action*	*Side Effects*
Gn-RH Analogues	Leuprolide, goserelin, buserelin, nafarelin acetate	Block pituitary LH secretion; decrease levels of T and DHT	Loss of libido, impotence, hot flashes, gynecomastia
Antiandrogens	Flutamide, nilutamide, casodex (ICI 176,334)	Block nuclear androgen receptor; do not decrease levels of T or DHT	Impotence in 10% to 15%, diarrhea in 10% to 20%, gynecomastia in 15%
5α-Reductase inhibitors...	Finasteride (MK-906), epristeride (SK&F 105657)	Block enzyme 5α-reductase, which converts T to DHT; do not decrease levels of T	Headache, no impotence, minimal loss of libido
Combined agents, progestational, antiandrogenic, and antigonadotropic effects	Cyproterone acetate, megestrol acetate	Block LH release and nuclear receptor androgen uptake	Impotence, loss of libido in 100%
Aromatase inhibitors	Testolactone atamestane	Block peripheral conversion of T to estrogen; do not decrease peripheral T levels	Occasional headache, no impotence or loss of libido

DHT = dihydroxytestosterone, Gn-RH = gonadotropin-releasing hormone, LH = luteinizing hormone, T = testosterone

receptors and the release of gonadotropin. A major disadvantage of the use of these agents is the reversibility of inhibition with time due to an override by rising levels of luteinizing hormone. Other disadvantages are a loss of libido and impotence due to lower levels of testosterone.

A new class of agents under trial for BPH is aromatase inhibitors. The physiologic basis for their use is the theory that BPH arises as a result of relative changes in the testosterone:estrogen ratio that occur in men with aging. This observation, coupled with the knowledge that estrogen stimulates BPH in canines, has initiated clinical trials with atamestane. Atamestane is a competitive and irreversible inhibitor of the steroid aromatase that is involved in the peripheral conversion of testosterone to estrogen. Initial observations with the use of this agent at the University of California, San Francisco, suggest that this drug has good tolerability, low toxicity, and does not impair libido. Efficacy results are as yet unknown.

Tables 5 and 6 summarize the currently available drugs in the United States for the treatment of BPH. There has recently been an explosion of interest in the medical management of BPH. Newer pharmacologic agents are being developed in parallel with a better understanding of the pathogenesis of BPH and its functional abnormalities. Several variables have produced heterogeneity of the disease process of BPH. These include the glandular versus the stromal components in the hyperplastic prostate, the dynamic versus the mechanical components, the lateral lobes versus the median lobe enlargement, and the hormonal status of a patient. As a result, a tailored approach for the medical management of BPH is still evolving. Techniques and agents under development such as endorectal magnetic resonance spectroscopy[57] and the ability to block α-receptors subselectively may allow further improvements in the management of prostatic disorders.

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Epitomes

Important Advances in Clinical Medicine

Chest Diseases

Anthony M. Cosentino, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in chest diseases. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Chest Diseases of the California Medical Association, and the summaries were prepared under the direction of Dr Cosentino and the panel.

Strategies for Home-Assisted Ventilation

THE GOALS FOR HOME-ASSISTED ventilation are to extend life, enhance the quality of life, provide an environment that enhances individual potential, reduce morbidity, improve physical and physiologic function, and reduce costs. The condition of a patient being considered for home-assisted ventilation must be reasonably stable, and there must be sufficient resources available in the community.

Specific indications for home-assisted ventilation include the following:

- Chronic respiratory insufficiency due to restrictive respiratory disorders—primarily neuromuscular and chest wall disorders. Long-term survival is excellent—70% to 80% of patients live for five years—and is associated with decreases in the number and length of hospital admissions for respiratory failure.
- Chronic hypoxia and hypercapnia in patients with chronic obstructive pulmonary disease (COPD). This includes patients who are weaned from assisted ventilation, but may benefit from nasal mask ventilation to treat persistent or worsening hypercapnia and patients who cannot be weaned from ongoing tracheostomy-assisted ventilation, but who are stable enough to be discharged to the community.
- Nocturnal oxygen desaturation and hypercapnia in selected patients without notable daytime hypoventilation syndromes such as obesity-related hypoventilation and "overlap" such as COPD and sleep apnea.

Tracheostomy-assisted techniques include volume-cycled or pressure-limited ventilation. These are preferred for patients with bulbar dysfunction, excessive tracheobronchial secretions, or upper airway obstruction when airway access is desirable. Body (negative pressure) ventilation is best used in patients with neuromuscular disorders without such complications. Nasal intermittent positive pressure has been used recently with best results in patients with neuromuscular weakness without airway or pulmonary parenchymal complications. This technique has uncertain results in patients with COPD.

In general, the long-term survival and quality of life of patients receiving home-assisted ventilation is better for those with neuromuscular and chest wall disorders than for patients with COPD. Recent studies suggest that patients on long-term home-assisted ventilation—most of whom have neuromuscular disease—consider noninvasive methods to be more convenient and to have less untoward effects on speech, appearance, and comfort than tracheostomy-assisted ventilation. The use of a cuffless tracheostomy with a one-way valve to facilitate speech, however, can still be used in those patients with severe respiratory impairment—that is, vital capacity of less than 1 liter—with appropriate adjustment of the tidal volume or pressure limit to compensate for the stomal leak.

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High-Resolution Computed Tomography

COMPUTED TOMOGRAPHY (CT) allows noninvasive, detailed viewing of chest anatomy. Because of its cross-sectional image display and superior contrast resolution, CT more sensitively detects and better evaluates abnormalities than chest radiography. High-resolution CT, defined by 1- to 2-mm sections reconstructed using a high spatial-resolution algorithm, further improves morphologic detail, largely by decreasing the averaging effects seen in stan-

dard 10-mm sections. "Thin-section" images have proved useful in a number of acute and chronic diseases of the lung and are a standard feature of all CT scanners.

The evaluation of acute nodular disease is aided by high-resolution CT when a surrounding halo of ground-glass attenuation is seen. Although the "CT halo sign" may be seen with any hemorrhagic nodule, whether infectious or neoplastic, in patients with neutropenia, this finding strongly suggests the diagnosis of invasive aspergillosis. In many acute lung diseases such as *Pneumocystis carinii* pneumonia and acute radiation pneumonitis, high-resolution CT can demonstrate early parenchymal abnormalities when other techniques give negative or equivocal results. False-positive results due to dependent atelectasis are reduced by the combination of prone and supine scanning.

In patients with chronic diffuse lung disease, a firm diagnosis is rarely provided by conventional radiography, and 10% to 15% may have a normal chest x-ray film. In several studies, high-resolution CT has demonstrated both a higher diagnostic sensitivity and specificity. Occasionally high-resolution CT findings may be so characteristic of a specific disease that therapy can be initiated without biopsy confirmation of the diagnosis. For example, reticular opacities in a predominantly subpleural and basilar distribution in a patient older than 50 years presenting with subacute dyspnea and restrictive functioning are generally sufficient for a diagnosis of usual interstitial pneumonia. The presence of nodular (interlobular) septal thickening with polygon formation is considered nearly pathognomonic of the lymphangitic spread of tumor.

In patients with chronic diffuse lung disease, areas of ground-glass opacification suggest active, possibly treatable disease and are the appropriate targets for biopsy. By providing a rough map and index of disease activity, that is, alveolitis versus fibrosis, high-resolution CT helps guide therapeutic decisions and limits biopsy site sampling errors. High-resolution CT also aids in choosing the best biopsy technique. Although transbronchial biopsy is appealing as a less-invasive technique than thoracoscopic or open-lung biopsy, it has a high yield only in diseases involving the lung tissue adjacent to bronchovascular bundles. The best examples are sarcoidosis and lymphangitic carcinomatosis. Most other chronic diffuse lung diseases usually require a surgical biopsy for definitive diagnosis.

Mild emphysema may be difficult to detect radiographically, even when suggested by the results of pulmonary function tests. High-resolution CT may show subtle emphysematous changes or bullous disease, thus explaining the pulmonary function abnormalities and directing appropriate therapy.

In patients with suspected bronchiectasis, thin-section images have supplanted bronchography as the best method for demonstrating airway dilatation, wall thickening, and mucous inspissation. Because bronchiectasis is often discovered in patients with hemoptysis, high-resolution CT is an important component of the diagnostic workup in patients with normal or inconclusive chest radiographic findings. The detection of bronchiectasis may also explain chronic cough or recurrent pneumonia not explained by conventional CT imaging or bronchoscopy. The demonstration of multifocal involvement appropriately identifies patients whose disease cannot be cured by surgical resection.

High-resolution CT is frequently added to conventional CT to further characterize focal abnormalities. In patients with diffuse lung disease, a dedicated high-resolution CT examination, consisting of 1- to 2-mm sections every 10 mm, is performed to obtain a representative sample of the lung parenchyma. The current indications for a dedicated high-resolution examination are as follows:

- To investigate signs and symptoms suggestive of diffuse lung disease in patients with normal or nonspecific chest radiographs;
- To investigate cases in which the chest radiographic abnormalities are not in keeping with the clinical presentation;
- To provide an index of disease activity, especially in patients with usual interstitial pneumonia;
- To determine the most appropriate type and site of lung biopsy;
- To diagnose bronchiectasis, and to determine its distribution.

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Preoperative Staging of Lung Cancer

STAGING OF LUNG CANCER is used primarily in patients with non-small-cell carcinoma. With rare exceptions, small-cell carcinomas, whenever discovered, are considered to have already metastasized and therefore are classified as stage IV.

The staging of non-small-cell lung cancer is based on the tumor-node-metastasis system first promulgated in 1974 and revised in 1986. Information required for staging includes the size and position of the tumor, the involvement of adjacent tissues by the tumor, the extent of regional lymph node involvement, and the presence and location of distant metastases. The stage correlates well with the prognosis, with or without treatment.

Preoperative staging is less accurate than the staging determined from tissue biopsies and actual exploration of the chest, but it provides invaluable assistance in selecting the most appropriate therapy. Preoperative staging not only identifies patients in whom thoracotomy would likely be

futile, but also detects its usefulness in situations in which a patient's condition may have originally seemed hopeless.

The status of a primary tumor in the lungs is most effectively studied by thoracic computed tomography (CT), which establishes the size and position of a tumor with precision. If a tumor is situated immediately adjacent to the chest wall or mediastinum, magnetic resonance imaging may be superior to CT in detecting invasion of these tissues. With centrally placed tumors, bronchoscopy will help determine resectability.

Although many surgeons depend on standard chest roentgenograms for evaluating the hilar and mediastinal nodes, thoracic CT with contrast enhancement has had an increasingly important role in this type of analysis. The usual practice has been to recommend mediastinoscopy if CT indicates that one or more nodes are enlarged and to advise exploratory thoracotomy without mediastinoscopy if the nodes are normal-sized. It has long been recognized that as many as half of the enlarged nodes are benign, and more recently it has been shown that 30% to 40% of nodes already involved with malignant spread appear normal in size. Some have suggested that a false-negative rate of this magnitude for CT would not warrant its routine use for staging nodes.

The new technique of positron-emission tomographic scanning shows promise of providing the highest sensitivity and specificity of all noninvasive methods for staging the hilar and mediastinal nodes and may well become the method of choice in the future. Because such scans include the entire body, they may prove to be the most cost-effective method for detecting widespread extrathoracic metastases.

The choice of techniques for detecting metastases depends largely on clinical clues suggesting focal disease. Techniques used include contrast CT scans or gadolinium-enhanced T1-weighted magnetic resonance images of the brain, bone scans, abdominal CT, and study of presumably malignant pleural effusions by thoracentesis and pleural biopsy. Although there is no clear consensus on using "routine" searches for metastases in the absence of focal signs, it is usual for the standard thoracic CT to be extended to include the liver and adrenal glands. In patients with isolated ipsilateral mediastinal or subcarinal nodal involvement (stage IIIA), routine organ scanning—brain, bone, liver, adrenal glands—is probably advisable because of the increased likelihood of metastasis.

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Primary Pulmonary Hypertension

IN THE PAST FEW YEARS our understanding of the diagnostic evaluation, prognosis, and treatment of primary pulmonary hypertension has grown. Noninvasive evaluation still includes an initial electrocardiogram and chest radiograph as screening studies. In affected patients, about 90% of chest x-ray films suggest the diagnosis of primary pulmonary hypertension. Doppler ultrasonography, when tricuspid or pulmonic regurgitation is present, can estimate pulmonary artery pressures and has largely supplanted periodic angiography to assess therapy. All patients should also undergo ventilation-perfusion scanning to identify the small subset of patients with chronic thromboembolic disease because recent studies of surgical pulmonary endarterectomy show superb results, with a surgical mortality of 8% to 9%.

Initial catheterization is still warranted both to confirm the diagnosis of primary pulmonary hypertension and to exclude left ventricular dysfunction and valvular and congenital cardiac causes. Pulmonary angiography is only useful in those patients with abnormal ventilation-perfusion scans, to search for surgically accessible, organized, proximal clots. Open-lung biopsies are rarely indicated.

Accrued data from the National Institutes of Health national registry of patients with primary pulmonary hypertension now provide us with clear prognostic indices. A right atrial pressure greater than 20 mm of mercury predicts a median survival of one month, compared with 46 months for a pressure of less than 10 mm of mercury. A pulmonary artery pressure of greater than 85 mm of mercury is associated with a median survival of one year, compared with 48 months for a pressure of less than 55 mm of mercury. Female sex, low cardiac output, and reduced mixed venous saturation also indicate a poor prognosis.

The therapy for primary pulmonary hypertension has evolved. Vasodilator trials, conducted with a Swan-Ganz catheter and arterial pressure monitoring, are useful for assessing patients' tolerance of vasodilators. Recent data showing that as many as 25% of patients with primary pulmonary hypertension respond to high doses of calcium channel blocking agents, particularly nifedipine, have added impetus to these studies. In patients who respond to therapy, pulmonary artery pressures will return to nearly normal, the right ventricular hypertrophy will subside, and they will live much longer.

A newer vasodilator agent, still not commercially available, is epoprostenol (prostaglandin I_2), also called prostacyclin. Given through a central venous catheter by continual infusion, epoprostenol prolongs survival in most patients with primary pulmonary hypertension and is therefore useful for those in whom calcium channel blockers are ineffective. Side effects include headache, flushing, and hypotension. A synthetic analogue of epoprostenol, iloprost, has a longer half-life and holds promise as a possible oral agent.

Nitric oxide gas (endothelium-derived relaxing factor) is also a potent vasodilator, but with a half-life of only a few seconds. Because of this, when given by inhalation, it achieves selective pulmonary vasodilatation. The chief stumbling block has been the absence of a safe and convenient method of delivery in its therapeutic range of about 2 to 40 ppm.

For patients for whom more conservative therapy is unsuccessful, heart-lung transplantation remains the best option. Accurate prognostic indices for primary pulmonary hypertension patients have improved our ability to allocate transplantation rationally. Three-year survival rates in the best centers are 60% to 75%. Experience with single- and double-lung transplantation in patients with remediable right ventricular function has also been encouraging in the past two to three years, with survival similar to that of heart-lung transplant recipients in selected patients.

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Selective Decontamination of the Gastrointestinal Tract to Decrease the Incidence of Pneumonia and Mortality

INFECTIONS ACQUIRED in critical care units contribute to morbidity, mortality, and costs. Nosocomial pneumonia is of particular concern because of the need for prolonged ventilator care and an associated mortality in excess of 50%. Many nosocomial infections are caused by gram negative, aerobic enteric pathogens that colonize the nasopharynx.

An early study attempted to decrease colonization in trauma patients on mechanical ventilation. The study used an oral paste of polymyxin B sulfate, amphotericin B, and tobramycin applied to the oral mucosa four times a day, an oral suspension of the same drugs given four times a day, and intravenous cefotaxime sodium. A substantial decrease in the incidence of colonization and a decrease in the infection rate occurred. Historical controls were used, and criteria for infection were imprecise. No mortality data were provided.

Additional studies have suggested that selective decontamination reduces the incidence of respiratory tract infections. Criteria for infection in most series were not rigid, however, and only a weak association between infection and reduced mortality was found.

A recent randomized, controlled study of gastrointestinal tract decontamination in 150 patients reported only 7 cases of pneumonia: 4 of 75 in the control group and 3 of 75 in the treatment group. Unlike other decontamination studies that reported a pneumonia-incidence rate of about 40%, this study made a diligent effort to precisely diagnose pneumonia. Fewer deaths occurred among the patients whose gastrointestinal tracts were decontaminated, but the difference was not significant.

Investigators in France reported no increase in survival rates among treated patients who received mechanical ventilation in intensive care units. Furthermore, the cost of care in the treatment group was raised. In this study also, a diagnosis of pneumonia was supported by results of bronchoscopy with protected-brush specimens, and the incidence of pneumonia was only 15% in the placebo group and 12% in the decontamination group. In the placebo group, pneumonia was more often caused by aerobic gram-negative organisms, and in the treatment group it was more often due to *Staphylococcus* species. Decontaminating the gastrointestinal tract may reduce the production of endotoxin and decrease mortality. This study found no decrease in the incidence of multiple organ failures.

A recent well-controlled study with rigid criteria for the diagnosis of pneumonia found no decrease in the incidence of pneumonia, mortality, length of hospital stay, or the duration of mechanical ventilation. The duration of mechanical ventilation in the patients was 4 to 22 days.

At present the data for selective decontamination of the gastrointestinal tract do not support the belief that it decreases the incidence of pneumonia and associated mortality.

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Tropical Lung Disease

RARE INFECTIONS, exotic parasitic illnesses, and unfamiliar genetic or environmental diseases, once considered limited to the tropical and subtropical world, are now appearing with increasing frequency in the emergency departments and outpatient clinics of North American and European hospitals. Several of these diseases primarily affect the lungs. Modern pulmonologists must learn how to diagnose and treat tropical lung disorders and be aware of the possibility of an imported illness in every visitor, tourist, political refugee, or newly arrived immigrant examined.

Tuberculosis continues to be the most important of all medical problems in tropical and other developing countries. The main concern in the differential diagnosis is to recognize the unusual patterns of tuberculosis seen particularly in older patients, in persons with immunosuppression, and in those with drug-resistant disease. Pulmonary melioidosis and paragonimiasis, both endemic in Southeast Asia, can produce clinical and radiographic features that resemble those of pulmonary tuberculosis. These two diseases should be considered in any patient suspected of having

tuberculosis but whose tuberculin skin test remains negative and whose sputum fails to show acid-fast bacilli on repeated examinations. A diagnosis of melioidosis depends on the identification of *Pseudomonas pseudomallei* in tissue fluids such as blood, sputum, pleural fluid, or pus or a positive serologic test of the organism. Pulmonary paragonimiasis, often referred to as endemic hemoptysis, can be diagnosed by showing ova in the sputum, stool, pleural fluid, or bronchoalveolar lavage fluid. Occasionally a transbronchial biopsy may reveal an adult fluke. A complement fixation test and other serologic studies, including immunoelectrophoresis, indirect hemagglutination test, indirect fluorescent antibody test with immunoglobulin (Ig) G, and IgG enzyme immunoassay, are useful.

Amebiasis, usually considered a disease of the tropics, is transmitted from person to person by the fecal-oral route. It now exists in every country of the world and should be considered in the differential diagnosis of any unexplained lower lobe pulmonary consolidation or pleural effusion. The response to treatment with metronidazole is so dramatic that it can be considered diagnostic. The presence of *Entamoeba histolytica,* either in the sputum, pleural aspirate, or aspirate from a hepatic abscess, establishes the diagnosis. Amebic gel diffusion, counterimmunoelectrophoresis, and indirect hemagglutination are accurate and extremely useful tests in nonendemic areas. Bowel infestation with *E histolytica* is common in endemic areas, and the organism may coexist with many other diseases. Similarly, the failure to detect *E histolytica* in a stool specimen does not exclude pleuropulmonary amebiasis.

Tropical pulmonary eosinophilia is seen mainly in India, Pakistan, Bangladesh, Southeast Asia, and the South Pacific islands. The clinical features of cough, fever, weight loss, night sweats, and diffuse miliary or nodular pulmonary infiltration are often confused with those of miliary tuberculosis, hypersensitivity pneumonitis, and sarcoidosis. In tropical eosinophilia, however, serum eosinophil counts and IgE levels are exceedingly high. The response to the administration of diethylcarbamazine citrate is dramatic and diagnostic.

Malaria and hydatid disease also affect the lungs. Clinical pulmonary disease develops in about 10% of patients with *Plasmodium falciparum* infection. Pulmonary edema and the adult respiratory distress syndrome are the two most serious, potentially lethal, complications. Diagnosis is made by examining a Giemsa- or Wright's-stained smear of peripheral blood. Hydatid disease in endemic areas is often included in the differential diagnosis of a localized nodular or a mass lesion in the lung. Occasionally a chest x-ray film may show multiple densities. A crescent or "water lily" sign, considered diagnostic, is caused by an air leak between the two membranes encircling the opacity; computed tomography and thoracic ultrasonography studies are helpful. A hydatid-specific, IgE enzyme-linked immunosorbent assay, immunofluorescent antibody, and indirect hemagglutination test increase chances of detecting pulmonary hydatid disease.

Other tropical diseases that involve the lungs include typhoid and paratyphoid infections, schistosomiasis, sickle cell disease, and hantaviral infections. Every physician needs to have a good knowledge of tropical pulmonary medicine to remain on guard when an unexplained lung or pleural lesion strikes an immigrant or a traveler returning from the tropics.

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Evaluating Patients With Chest Pain

CHEST PAIN is a common symptom in patients seen in emergency departments and in inpatient and outpatient settings. The primary concern of both clinician and patient is to exclude a cardiac origin, possibly the most life-threatening. The mainstay of chest pain evaluation after a careful, focused history is not the electrocardiogram (ECG), but the noninvasive stress test.

An understanding of Bayes' theorem is essential to the rational, cost-effective use and accurate interpretation of noninvasive stress testing in the diagnosis of coronary artery disease. According to Bayes' theorem, the positive and negative predictive values of a test are determined not only by test specificity and sensitivity, but also by the prevalence of the disease in patients similar to those under consideration. In estimating the probability of coronary artery disease in a given patient, a clinician uses features of clinical history—including the presence or absence of the standard risk factors for the disease—and physical examination. The sensitivity and specificity of treadmill exercise testing, the most common form of stress testing, are determined by several factors, including the ECG definition of an abnormal (positive) test result, achieved double product (systolic blood pressure times heart rate), and metabolic equivalent units (METs) or resting oxygen intake (usually 3.5 ml of oxygen per kg per minute), duration of exercise, and underlying ECG abnormalities that might preclude a meaningful interpretation of exercise tracings. Exercise scintigraphy, echocardiography, and radionuclide angiography are useful in overcoming the difficulty that baseline ECG abnormalities impose on interpreters. Stress scintigraphy or echocardiography using pharmacologic agents such as dobutamine or dipyridamole are particularly useful in patients unable to achieve a reasonable double product with dynamic exercise or who cannot exercise because of musculoskeletal problems, amputation, or limiting claudication.

In patients with typical angina pectoris in whom the probability of coronary artery disease is high, the exercise

test provides only modest incremental value in establishing the diagnosis; it can, however, provide important prognostic information based on the non-ECG variables of exercise duration and METs achieved, as well as data that may indicate the need for coronary arteriography. Whereas establishing a diagnosis of coronary artery disease requires the achievement of an adequate heart rate, evaluating the effect on myocardial ischemia of a particular antianginal regimen need not, and the patient may exercise while taking all relevant medications.

Determining the diagnosis in a patient with chest pain atypical for ischemia can be a challenge. The probability of coronary disease in these patients ranges from 10% to 70%, affecting both the positive and negative predictive value of the exercise test result. The sensitivity and specificity assume a more important role; more stringent criteria to define an abnormal test result become necessary for meaningful interpretation. Here, too, high achieved heart rate and high-level and long exercise duration indicate a benign prognosis, whatever the exercise ECG shows. Further evaluation need not be undertaken, although close follow-up is recommended.

If patients achieve greater than 85% of their age-predicted maximum heart rate, yet cannot perform prolonged exercise and have evidence of ischemia, exercise scintigraphy or echocardiography is recommended to assess the volume and areas of myocardium at ischemic risk. If a notable perfusion defect or a wall-motion abnormality is noted, consideration should be given to coronary arteriography. If a substantial perfusion defect or wall-motion abnormality is not found, close follow-up and periodic treadmill tests are recommended. If patients have evidence of ischemia and do not achieve 85% of maximum predicted heart rate or cannot perform prolonged exercise, coronary arteriography is generally indicated. Pharmamacologic stress scintigraphy or echocardiography is used if baseline ECG abnormalities or limited exercise capacity precludes the use of standard treadmill testing.

Because of the perception that women have a high "false-positive" rate on standard treadmill exercise testing, using coronary angiography as the gold standard, routine stress scintigraphy has been advocated in female patients. Our practice is to do the less costly, standard exercise test first. If an ischemic test shows no abnormality, the patient is reassured of the absence of important myocardial ischemia, and no further workup is undertaken. If an ischemic test results, the patient is considered to have angina and is appropriately treated. Should coronary arteriography be done and the angiogram results are normal, the diagnosis of microvascular angina (syndrome X) should be strongly considered and the patient treated with appropriate antianginal medication. A normal coronary angiogram does not exclude the diagnosis of myocardial ischemia.

Patients with chest pain in whom both exercise ECG and scintigraphic results are normal have a benign prognosis despite the continuation of their chest pain. Reassurance in these cases is appropriate, and treatment is continued for the chest pain, if necessary.

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Alerts, Notices, and Case Reports

Porphyria Cutanea Tarda and Hepatitis C Virus Infection in a Patient With Acute Liver Failure

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PORPHYRIA CUTANEA TARDA, the most common form of porphyria in the world,[1] is caused by decreased activity of the enzyme uroporphyrinogen decarboxylase.[2] This enzyme defect either can occur sporadically or can be inherited in an autosomal dominant manner.[3] It is characterized by skin hyperpigmentation, vesicles, hypertrichosis, and easy bruisability.[4] Most patients with the disorder have evidence of chronic liver disease, ranging from steatosis to chronic active hepatitis to cirrhosis.[5-7] The cause of these liver abnormalities is unknown, but previously had been attributed to the effects of alcohol, iron overload, or both.[8]

New data have recently shown that the presence of hepatitis C virus (HCV) is the single most common hepatic abnormality in patients with porphyria cutanea tarda.[9-11] It has been proposed that HCV may play a critical role in the pathogenesis of liver disease associated with porphyria cutanea tarda.[9-11] We report an interesting case of a patient with HCV and acute hepatocellular necrosis in association with newly symptomatic porphyria cutanea tarda.

Report of a Case

The patient, a previously healthy 43-year-old man, was seen because for three weeks he had had anorexia, lethargy, myalgia, and intermittent right upper quadrant pain. A week before admission, he also noted dark brown urine, bilious emesis, and new hyperpigmentation of his face, neck, and hands, with multiple blisters on the palmar surface of his hands and fingers.

There was no history of blood transfusions, arthralgias, melena, intravenous drug use, exposure to ill persons, previous hepatitis, or similar skin lesions. He had been taking acetaminophen, as much as 3 grams per day, for the preceding seven days as treatment of his abdominal pain, but was not taking any other medications. He had stopped drinking his usual three alcoholic drinks per day a month before admission. He grew up in Fiji, emigrated to the United States eight years ago, and has been employed as an automobile mechanic. He had no family history of dermatologic diseases.

On physical examination on admission, the patient appeared acutely ill, with a temperature of 38°C (100.4°F), pulse rate 100 beats per minute, blood pressure 137/70 mm of mercury, and a respiratory rate of 22 breaths per minute. He had moderate right upper quadrant tenderness without peritoneal signs, normal bowel sounds, and a nonpalpable spleen. The liver span was estimated at 12 cm by percussion. Increased pigmentation was present on the face, hands, and neck, and multiple bullae and erosions were observed on the palmar and dorsal surfaces of both hands. He had no stigmata of chronic liver disease, and the findings of the rest of the examination were normal.

Blood chemistry values on admission included normal electrolytes and renal function tests. A serum glucose level was 9.0 mmol per liter (162 mg per dl); serum total protein, albumin, calcium, phosphorus, uric acid, and amylase values were all normal; and alanine aminotransferase (ALT) was 709 and aspartate aminotransferase (AST) 1,531 units per liter; transaminase levels throughout his hospital course are shown in Figure 1. Total bilirubin was 59.9 μmol per liter (3.5 mg per dl), and alkaline phosphatase was 229 units per liter; neither value changed appreciably during his hospital stay. A

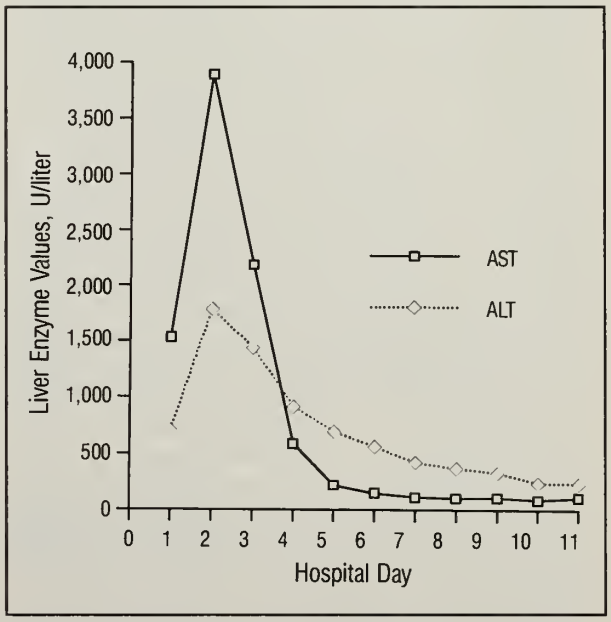

Figure 1.—The graph shows the patient's serum transaminase levels during his hospital course. ALT = alanine aminotransferase (normal, 7 to 56 U/liter), AST = aspartate aminotransferase (normal, 5 to 35 U/liter)

(Jasmer RM, Larson MS, Weilbaecher KN: Porphyria cutanea tarda and hepatitis C virus infection in a patient with acute liver failure. West J Med 1994; 161:513-515)

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ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
AST = aspartate aminotransferase
HCV = hepatitis C virus
Ig = immunoglobulin

lactate dehydrogenase level on admission was 6,861 units per liter.

The leukocyte count was 10.2×10^9 per liter (10,200 per mm^3) with a normal differential, hematocrit 0.37 (37%), and platelet count 105×10^9 per liter (105,000 per mm^3). A prothrombin time on admission was 15.6 seconds (international normalized ratio 2.38); subsequent prothrombin times are displayed in Figure 2. A urinalysis disclosed dark brown urine with 3+ bilirubin and normal findings on microscopic examination. An ultrasound examination of the right upper quadrant revealed no extrahepatic or intrahepatic ductal dilatation or gallstones.

The patient was given a presumptive diagnosis of acute hepatitis with skin lesions strongly suggestive of porphyria cutanea tarda. *N*-Acetylcysteine was given empirically 18 hours after admission, although an acetaminophen level measured at that time was less than 30 mmol per liter.

On the second hospital day, a grade II hepatic encephalopathy developed, characterized by drowsiness, disorientation for time, and asterixis, and the patient was transferred to the intensive care unit. His serum ammonia level peaked at 48 μmol per liter on the third hospital day. Further workup disclosed a positive second-generation enzyme-linked immunosorbent assay for HCV (EIA 2.0, Abbott Laboratories, Abbott Park, Illinois), which was confirmed by a positive recombinant immunoblot assay (RIBA II, Nichols Institute, San Juan Capistrano, California). In addition, the patient's serum tested positive for HCV RNA by polymerase chain reaction (Roche Molecular Systems, Branchburg, New Jersey). Immunoglobulin (Ig) M-specific antibody test to hepatitis A virus was negative, as were tests for hepatitis B surface antigen and IgM-specific antibody to hepatitis B core antigen. Other workup included a serum ferritin level of 53,900 μg per liter (53,900 ng per ml), iron 33 μmol per liter (182 μg per dl), iron-binding capacity 45 μmol per liter (252 μg per dl); antismooth muscle antibodies were not present, and a ceruloplasmin level was normal. An antibody test for the human immunodeficiency virus was negative.

Urine uroporphyrin levels were measured on the patient's second hospital day: uroporphyrin, 20,145 μg per 24 hours (normal 0 to 57); coproporphyrin, 5,036 μg per 24 hours (normal 32 to 267); and porphobilinogen, 0 (normal) (Nichols Institute, San Juan Capistrano, California).

His liver function (Figures 1 and 2), skin lesions, and overall clinical status improved remarkably with supportive care alone. He was discharged on the 11th hospital day. He did not return for follow-up examination.

Discussion

Porphyria cutanea tarda, caused by reduced activity of uroporphyrinogen decarboxylase, can be inherited in an autosomal dominant manner or can occur sporadically.[3] That its clinical expression is variable and that most patients with the disorder have some form of underlying liver disease led to the theory that liver injury unmasks the enzyme defect of porphyria cutanea tarda.[9] The spectrum of underlying hepatic disease includes steatosis, chronic active hepatitis, cirrhosis, and hepatocellular carcinoma.[5-7] The recognized agents of liver injury in patients with the disorder include alcohol,[12] estrogens,[12] and toxins such as hexachlorobenzene.[13]

Several recent studies have shown that HCV infection, detected serologically or by polymerase chain reaction, is present in as many as 80% of patients with porphyria cutanea tarda.[9-11] The reasons for this high prevalence of HCV infection are unknown, as most patients do not have risk factors such as a history of previous blood transfusions or injection drug use.[9,10] We demonstrated HCV infection in our patient, who had no known risk factors, by both positive serologic tests and polymerase chain reaction.

Hepatitis C virus infection is likely the most relevant pathogenic factor of liver disease in patients with porphyria cutanea tarda. This is based on the following observations:

- Evidence of HCV infection has been found in 80% of these patients[9,10];
- Patients with porphyria cutanea tarda with antibodies to HCV have significantly higher serum aminotransferase levels than patients with porphyria cutanea tarda but without HCV antibodies[9,11];

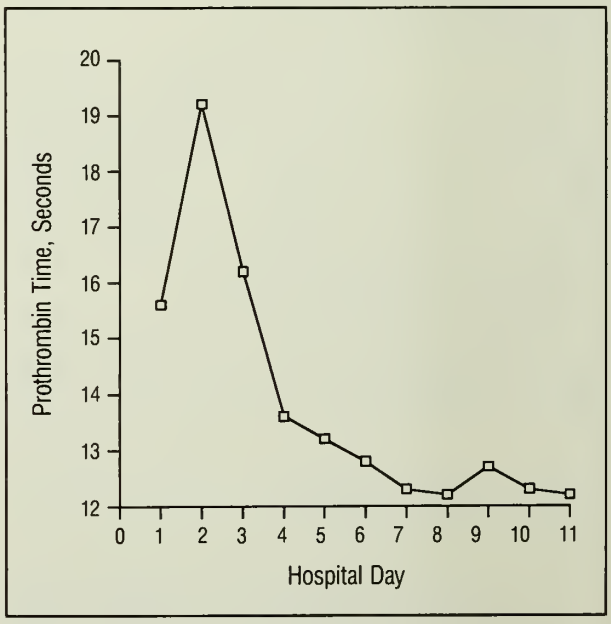

Figure 2.—The graph shows the patient's prothrombin times (PT) during his hospital course (control PT each day was 12.3 seconds).

• The prevalence of antibodies to HCV has correlated with the severity of liver disease on histologic examination."

Our patient's clinical course was particularly interesting because he had the development of acute liver failure in association with newly symptomatic porphyria cutanea tarda. By self-report, our patient had a long history of three drinks of gin per day, although he said this practice had stopped three weeks before admission. He began taking acetaminophen as treatment of his abdominal discomfort. This discomfort may have represented subacute liver injury, such as from alcohol or HCV infection.

His acute liver damage at presentation was consistent with the often-overlooked syndrome of therapeutic acetaminophen hepatotoxicity in patients with chronic alcohol use: the markedly elevated AST level above 1,000 units per liter, an AST:ALT ratio of greater than 2, and a normal acetaminophen concentration in a patient taking therapeutic doses of acetaminophen.[14,15] Our patient's greatly elevated serum ferritin level may have been due to acute hepatocellular necrosis, but could have also reflected an underlying iron storage disease such as hemochromatosis. Further diagnostic testing was not possible, because the patient did not return for further evaluation.

The presence of HCV infection in this patient raises several issues. Currently available tests for HCV do not allow an accurate distinction of acute from chronic infection. Hepatitis C virus usually causes chronic liver disease[5-7]; its role in acute hepatocellular necrosis is controversial.[16-18] In this case, HCV may have contributed to a chronic liver injury, a subacute injury, or less likely, acute liver injury. The virus likely modified the hepatic milieu and perhaps the expression of porphyrins such that in a patient with acute hepatocellular necrosis (probably due to therapeutic acetaminophen toxicity), porphyria cutanea tarda became manifest.

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Pulmonary Tuberculosis, Amenorrhea, and a Pelvic Mass

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THE WORLD HEALTH ORGANIZATION estimated that there were about 8 million new cases of tuberculosis and 2.9 million deaths from tuberculosis worldwide in 1990.[1] Furthermore, from 1985 through 1992, the number of tuberculosis cases reported in the United States has increased by 20%.[2] Infection with the human immunodeficiency virus (HIV), increased immigration from areas endemic for tuberculosis, the decline of public health institutions, and worsening socioeconomic conditions have all contributed to the national rise of tuberculosis.[2] Of the 25,701 new cases of tuberculosis diagnosed in the United States in 1990, pulmonary tuberculosis accounted for 82% of these new cases, and 5.1% of the patients had both pulmonary and extrapulmonary tuberculosis.[3] Among these cases of tuberculosis in the United States, only 399 (1.6%) involved the genitourinary tract.[3] We report a rare case of pelvic tuberculosis that developed and presented as an unusually large mass simulating pregnancy during treatment of active pulmonary tuberculosis. We also review the common clinical manifestations, diagnosis, and treatment of pelvic tuberculosis.

(Wehner JH, De Bruyne K, Kagawa FT, et al: Pulmonary tuberculosis, amenorrhea, and a pelvic mass. West J Med 1994; 161:515-518)

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ABBREVIATIONS USED IN TEXT

AFB = acid-fast bacilli
HIV = human immunodeficiency virus

Report of a Case

The patient, a 31-year-old woman, was admitted to the hospital for suspected multidrug-resistant pulmonary tuberculosis. Five years before admission, she emigrated to the United States from the Philippines and was noted to have a positive tuberculin skin test with a normal chest roentgenogram. She was given isoniazid, which she took for only three of the recommended six months. Five months before admission, she was seen by a local physician because of fever, cough without hemoptysis, anorexia, and a 12-kg (27-lb) weight loss during the preceding two months. Her chest roentgenogram revealed extensive bilateral pulmonary infiltrates. Sputum specimens were positive by smear and culture space for *Mycobacterium tuberculosis* that was sensitive to all drugs. A regimen of isoniazid, 300 mg a day; rifampin, 300 mg twice a day; and pyrazinamide, 500 mg twice a day by mouth, was started. She took only some of these medications daily for three months, in split doses, until she ran out of them a month before admission. She subsequently lost her job, and her care was transferred to a public health physician who recommended she be admitted to a hospital to rule out multidrug-resistant tuberculosis.

On admission, the patient said she did not have cough, fever, or night sweats. Her appetite was slightly improved, but she had gained only 1.4 kg (3 lb) in weight. She noted, however, that her abdomen had progressively enlarged during the previous four months and that her last menstrual period was five months before admission. Her menses had always been irregular, coming every one to two months. She had a cesarean section three years previously and had not been pregnant since then. Furthermore, she had not had sexual relations in more than two years.

On the initial physical examination, the patient was thin and afebrile. Her lungs were normal to auscultation, and examination of the heart revealed a 2/6 systolic flow murmur. The abdomen was soft, with normal bowel sounds and without hepatosplenomegaly. A large, smooth, slightly tender, nonmobile pelvic mass was palpated extending to the level of the umbilicus. The pelvic examination revealed no vaginal discharge or cervical motion tenderness. There was no peripheral lymphadenopathy.

Laboratory tests elicited the following values: leukocyte count, 16.8×10^9 per liter (16,800 per mm^3), with 0.76 neutrophils, 0.12 lymphocytes, 0.09 mononuclear cells, and 0.03 eosinophils; hematocrit, 0.23 (23%); urea nitrogen, 4.3 mmol per liter (12 mg per dl); and creatinine, 115 μmol per liter (1.3 mg per dl). A urinalysis showed 4 to 10 leukocytes per high-powered field, and a urine culture was negative for nontuberculous bacteria. A serum pregnancy test and an HIV antibody test were both negative. A serum CA 125 tumor-associated antigen level was mildly elevated at 44.9 U per ml (normal, 0 to 34). A repeat chest roentgenogram showed substantial improvement compared with the initial film. Magnetic resonance imaging of the pelvis revealed an extrauterine pelvic mass measuring 13.0 by 13.3 by 11.9 cm (Figure 1). Numerous fingerlike interdigitations were seen with enhancing nodular opacities extending inward from the mass wall (Figure 2). In addition, the ureters were obstructed bilaterally with secondary hydronephrosis. The right ovary was partially surrounded by the mass, and the left ovary was not visualized. There was no notable ascites or lymphadenopathy.

A sputum smear was positive and three urine specimens were negative for acid-fast bacilli (AFB). Therapy with oral isoniazid, rifampin, and pyrazinamide was restarted. In addition, because of the fear of drug resistance from her inconsistent use of antituberculosis medications, two new agents, ethambutol hydrochloride and ciprofloxacin hydrochloride, were added to what was presumably a failing drug regimen. Fine-needle aspiration of the pelvic mass revealed 4+ AFB on a smear. Because of recurrent fevers to 39°C (102.2°F) and a persistently elevated serum creatinine level to as high as 150 μmol per liter (1.7 mg per dl), a transcutaneous drainage catheter was placed in the tuberculous abscess, which drained 800

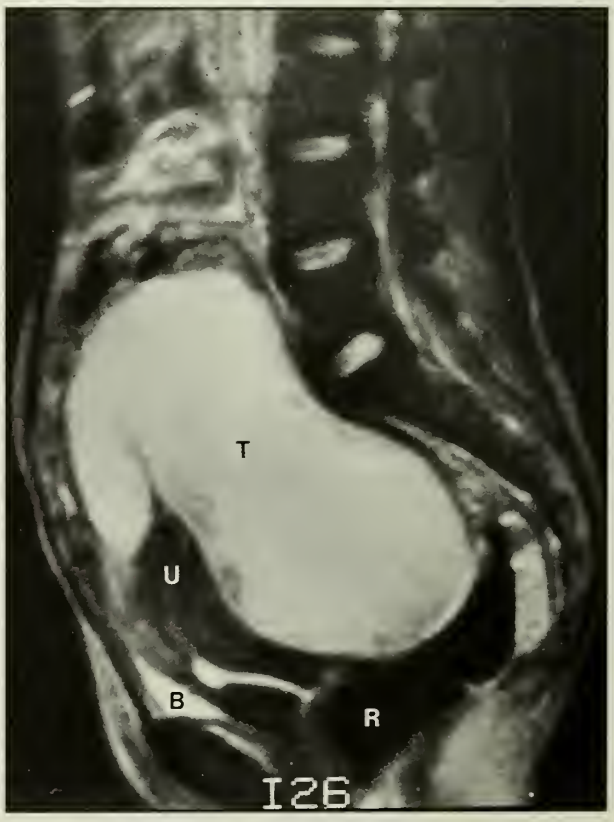

Figure 1.—A midline sagittal T2-weighted magnetic resonance imaging scan of the pelvis depicts a tuberculous abscess (T) that appears to originate within the pelvis and extends into the lower abdomen anterior to the uterine fundus (U). R = rectum, B = bladder

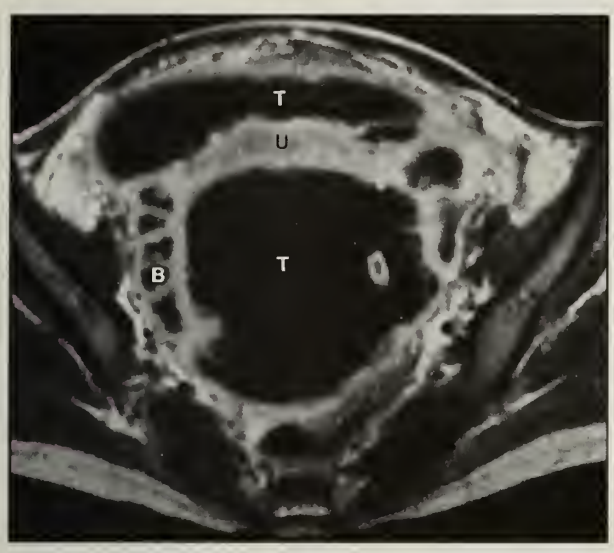

Figure 2.—A transverse, gadolinium-enhanced, T1-weighted magnetic resonance imaging scan reveals numerous fingerlike interdigitations and enhancing nodular opacities extending inward from the abscess wall. Adhesions to adjacent small bowel (B) are also shown. T = tuberculosis abscess, U = uterus

ml of purulent material over a six-day period. Ureteral stents were placed on both sides prophylactically for possible stricture. Thereafter, the patient defervesced and the serum creatinine level returned to normal. Finally, in view of the large AFB burden within the abscess, a third agent, capreomycin sulfate, was added until the results of a retesting of sensitivities were available.

On hospital day 24, the patient was discharged home on directly observed therapy. After eight weeks, all sputum and urine cultures, as well as the pelvic abscess culture, were negative for *M tuberculosis*. She is currently asymptomatic and has begun to menstruate.

Discussion

Genital tuberculosis is nearly always a result of dissemination from a primary source, most commonly the lungs. Infection may occur through hematogenous or lymphangitic spread, as well as direct extension from tuberculous abdominal viscera.[4] In 90% to 100% of cases, both fallopian tubes are diseased. From the diseased fallopian tubes, the tuberculous infection then spreads to the endometrium of the uterus in 50% to 60% of patients, and direct extension to the ovaries occurs in 20% to 30%. Tuberculosis of the cervix and vagina is less common.[4] Rarely, female genital tuberculosis can be acquired sexually from an infected partner with active genitourinary tuberculosis.[5] The lack of substantial ascites and abdominal adenopathy and the inability to identify the left ovary distinctly all suggest that our patient's tuberculous abscess originated from tuberculous salpingitis rather than peritoneal tuberculosis.[6]

Infertility clinics worldwide have reported an incidence of pelvic tuberculosis ranging from 1% in Australia to 19% in India, with a mean of 5% to 10%.[4] Among women of childbearing age who have active pulmonary tuberculosis, as many as 13% may have concomitant genital tuberculosis.[7] In a review in 1976 it was reported that 80% to 90% of cases of genital tuberculosis occurred in patients aged 20 to 30 years.[4] Authors have since shown an increasing incidence in women older than 40 years.[8-10]

Female patients most often present with primary or secondary infertility (13% to 55%), pelvic or abdominal pain (25% to 50%), abnormal uterine bleeding (11% to 41%), postmenopausal bleeding (2.8% to 8.4%), and amenorrhea (<2%).[4,8-10] Of 187 patients with genital tuberculosis, 11% were completely asymptomatic.[8] To our knowledge, our patient's is the largest reported mass due to genital tuberculosis and the first masquerading as a pregnancy. As in this patient, a history of tuberculosis can be obtained from 3% to 50% of patients.[4,8,10] Investigators noted that abnormal menstrual cycles, including amenorrhea, occurred frequently in patients both with and without genital tuberculosis. It was concluded that pulmonary tuberculosis indirectly affected the genital tract in most cases.[7] Physical findings can be normal in at least 43% of patients with genital tuberculosis.[10] Pelvic masses are found in 15% to 47% and are usually tubo-ovarian in origin.[7-11] Chest roentgenograms may be normal in 40% to 80% of patients with genital tuberculosis.[10,11]

Because presenting symptoms are nonspecific and are suggestive of more common nontuberculous clinical conditions—pelvic inflammatory disease, uterine fibroids, endometriosis, malignancy, ectopic pregnancy, and infertility—pelvic tuberculosis is usually not considered as a possible diagnosis. Instead, pelvic tuberculosis is often diagnosed retrospectively after specimens of extirpated tissue reveal granulomas. If, on the other hand, pelvic tuberculosis is suspected, histologic examination of specimens of premenstrual endometrial biopsies, curettage, or both may yield granulomas in 50% to 70% of patients.[4,8] Cultures of endometrium and menstrual blood may be positive for tuberculosis in 30%.[8] Repeated examinations of menstrual blood may be required, however.[12] In one report, urine cultures were positive in 18 (3.5%) of 510 patients with genital tuberculosis.[11] Diagnosis by percutaneous needle aspiration, as was done in our patient, has not been previously described.

Hysterosalpingography is usually abnormal among infertile patients with genital tuberculosis.[4,10] Although tuberculous salpingitis has characteristic radiographic findings, tubal diverticulosis, tubal endometriosis, and bacterial tubal obstruction may have similar appearances.[13,14] Thus, tissue or confirmatory cultures are recommended to establish the diagnosis of genital tuberculosis.[4]

Among patients with pelvic-adnexal masses, the serum level of the tumor-associated antigen, CA 125, has been used to help discriminate malignant from benign gynecologic conditions.[15] Although usually clinically useful as a diagnostic adjunct, reports have documented substantially elevated CA 125 levels in the serum of patients with pelvic and peritoneal tuberculosis, which declined to normal levels after treatment.[16] Our patient's mildly increased CA 125 level was probably due to genital tuberculosis.

The mainstay of treatment, as in pulmonary tuberculosis, is combination chemotherapy. Current treatment recommendations for genital tuberculosis should follow similar guidelines as for pulmonary tuberculosis.[17,18] For pansensitive organisms, a six-month course of isoniazid and rifampin combined with pyrazinamide for the initial two months should be adequate. Unless the local prevalence of isoniazid resistance is low, ethambutol should be added to the initial treatment regimen until sensitivities are known.[17-20] If isoniazid resistance is confirmed, then rifampin, ethambutol, and pyrazinamide therapy should be continued for a total of at least six months.[17] Because progressive disease developed in our patient while she was taking intermittent antituberculous therapy, three new agents—ethambutol, ciprofloxacin, and capreomycin—to which her organism was presumed susceptible, were added in accordance with the 1993 Centers for Disease Control and Prevention and American Thoracic Society recommendations for initial therapy in patients with suspected multidrug resistance.[20] In addition, all patients at risk for noncompliance or in locales with low treatment completion rates should be considered candidates for directly observed therapy.[20]

Follow-up endometrial biopsies and cultures are recommended.[11] Despite the fact that the tuberculous abscess and the sputum were smear-positive for AFB, the subsequent cultures surprisingly did not grow mycobacteria. The most likely explanation is that the organism remained sensitive to the original antituberculous regimen, as evidenced by improvement on the chest roentgenogram, and the abscess expansion was a paradoxical phenomenon, as is occasionally reported in other extrapulmonary sites of infection.[21-24]

As the drug regimens have improved, the need for surgical intervention has declined.[11] The indications for surgical treatment are persistent or recurrent pelvic pain, the development or persistence of large adnexal masses, a recurrence of endometrial infection, and a recurrence of excessive uterine bleeding.[11] A minimum six-month course of chemotherapy preoperatively has been recommended. Furthermore, the operation should completely remove the fallopian tubes, uterus, and ovaries, regardless of age.[11] In our patient, the gynecologists elected to defer a surgical procedure by placing a percutaneous drain to decompress the pelvic mass.

When medical treatment is completed, subsequent successful full-term pregnancy appears unlikely, but possible. After extensively reviewing the literature, one author concluded that in the presence of advanced disease, patients should be considered permanently infertile.[4] In a series of 84 pregnancies among 710 patients, only 35 (41%) successfully delivered. In contrast, there were 21 abortions, 26 ectopic pregnancies, and 2 neonatal deaths.[11]

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Commentary

We Tried It Once

Recollections of an Early Government Health Care Program

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Memories of events that occurred half a century ago may not be accurate in all details, and verification is all but impossible, but my memories of certain experiences with a federal health care program when I was serving a locum tenens in a small eastern Oklahoma town (Sapulpa) remain quite vivid. This program illustrates some of the basic problems that can arise in such centrally financed programs.

In early 1941 this region of Oklahoma was still reeling from the effects of the Great Depression of 1929 and from the dust storms that devastated so many thousands of acres of Midwest farmland. The farmers were among the hardest hit, and their medical care was poor to nonexistent. As a result, counties named practicing physicians as county physicians and paid them small annual stipends to render care to indigent patients in their area of the state. Nonemergency patients requiring admission to hospital could be referred, on approval, to the state hospital in Oklahoma City, some 120 miles away. The county physician arrangement was far from satisfactory. Calls from indigent patients were answered after physicians' paying patients were cared for. In addition, as older physicians, county physicians often had finished medical school at one of the diploma mills before the revolution in medical education that followed the Flexner Report.

The indigent patients might have been poor, but they were not stupid. They had long ago ceased to have any confidence in these county physicians' medical ability, consulting them only as a last resort. Indigent patients preferred to see one of the other physicians in town, even if it meant promising to pay a $2 charge when money was available—and it rarely became available—and sitting in the waiting room, at times for half a day, until all the other patients had been treated. Needless to say, most illnesses were treated with home remedies until they ran their course or became serious enough to require admittance to a hospital. Limited funds were available at the local hospital for brief hospital stays for these patients. Longer illnesses required transfer to a state hospital.

In this setting the Federal Farm Bureau—one of its many names over the years—established one of the first programs conducted by the federal government to provide a single payer-capped system of health care. Recognizing the desperate plight of these indigent farm families, the government initiated a federally financed program to provide them with basic medical care. Each state was allocated a certain sum of money based, I suppose, on the estimated number of such families. These funds were then, in Oklahoma at least, distributed to the various counties, again based on need. At the county level the allocation was divided into monthly amounts.

In the first weeks of the program, both the farmers and the physicians were delighted. The farmers found they could consult the physician of their choice and were no longer placed in the back of the room to be seen after all of the other patients. The physicians found that the charges for these services, which had previously been largely written off, were now paid in full, and promptly, by the Bureau.

Unfortunately, this utopian solution was not to last long, and herein may be found some fundamental flaws in that early effort pertinent to any future health care plan. The first downward step came when these poor, previously underserved families began to recognize that some form of medical care was now readily available without charge, and consultations were sought for previously neglected but appropriate health problems. The volume of these unmet needs was grossly underestimated in the original funding. Added to this deficit came another unforeseen factor, an example of the well-known "insatiable appetite" of the public for medical care. Recognizing that they were not only admitted but actually welcomed to physicians' waiting rooms, a trip into town was not complete until nearly every member of the farm family had been examined and a bottle of medicine obtained from the nearby drugstore. Obviously such a demand soon overwhelmed the monthly allocation, and in an effort to honor all of the bills submitted, payments were prorated to fit within the money available for the month. Instead of paying each bill at 100 cents to the dollar, payment was reduced to, say, 95 cents for each dollar billed.

The second downward step followed rather quickly. Physicians, recognizing that their bills were going to be discounted, quietly added the anticipated discount to their bill. In other words, what had been a $2.00 charge for an office visit now became a $2.50 charge. In an effort to con-

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trol the snowballing effect as the prorated payments of these continuously inflated charges became smaller and smaller, one of the first attempts to use a professional standards review organization mechanism was instituted. Two small towns (Sapulpa and Bristow) of about equal population and with about the same number of physicians supplied most of the medical care for the entire county, so with the assistance of the county medical society, a confidential review committee was established in each town. Charges submitted by physicians in Sapulpa each month were reviewed for their appropriateness by the committee in Bristow, and vice versa. Such a review resulted in some modest control of the rapidly escalating costs, but despite continued efforts by the Bureau and the county and state medical societies, the program ended in bankruptcy. Shortly thereafter, the surging economy associated with the entry of the United States in World War II improved farm incomes somewhat and also offered the most marginal farmers an opportunity to earn a livelihood elsewhere.

What might we learn from this long-forgotten attempt at governmental health care, stripped as it was of some of today's compounding factors such as high-tech care, insurance, and administrative costs and legal fees? First, it is financially impossible for any society to provide unlimited health care to its entire population. Restrictions of some type must accompany any plan. But even with such restrictions, the costs must not be underestimated, and realistic budgeting must be in place for any plan to succeed.

Second, the human elements in the equation must not be overlooked—the enormous need perceived by the public for medical attention and the natural impulse of physicians and other health care professionals, as the change is made from one system of medical care to another, to preserve an acceptable level of remuneration. The response of the professionals to the Clinton health care plan recalls a similar reaction when the Medicare program was introduced. The marginal health care that had been rendered to older indigent patients with little hope of compensation before Medicare was now partially paid for, and the costs of the program, in part because of unanticipated demand and in part because of gradually rising provider and other charges, have far exceeded the original estimated expenditure.

We have gained extensive experience with large, federally financed and conducted programs in the past century, but few if any such programs will compare in complexity and size with that which we are now contemplating. As we look forward to the development of a program designed to provide health insurance for everyone, the lessons of a bygone era should not be forgotten.

Editorials

Pharmacologic Management of Benign Prostatic Hyperplasia—Changing Times

THIS PERIOD OF MEDICAL HISTORY has been officially designated as the "Decade of the Brain," but from the perspective of a urologist, it feels much more like the "Decade of the Prostate." Elsewhere in this issue of THE WESTERN JOURNAL OF MEDICINE, Drs Narayan and Indudhara comprehensively review a fascinating aspect of this history—the evolution of medical therapy for benign prostatic hyperplasia (BPH).[1] Benign prostatic hyperplasia makes up one arm of the triad of prostate cancer, prostatitis, and BPH that affects the prostates of aging men. This disease serves as a link between man and man's best friend, the dog, as the only two mammals in whom the malady is knowsn to develop.[2] Until recently, it was a disease whose treatment was relegated almost exclusively to the use of surgical therapy and, in particular, transurethral resection of the prostate (TURP). After cataract surgery, this operation remains the second most common and most costly surgical procedure under Medicare. In 1986 it constituted 36% of urologists' surgical load.[3,4] The incidence rate for surgical therapy for BPH in the United States for 1990 of 13 per 1,000 men is one of the highest in the world.[5] More recent Medicare data show, however, that the use of TURP is on the decline, down nationally almost 18% in 1992 from a peak of 253,000 operations in 1987.[4] Our own experience at the University of New Mexico School of Medicine would suggest that this figure may be closer to 50% based on TURP numbers for 1993. Much of the decline in surgical therapy is attributable to the use of medical therapy for the disease, and as this article makes clear, times are changing.

Ten years ago, urologists argued about the most appropriate way to manage prostate cancer, but there was a general consensus about the treatment strategy for BPH. Ten years later, urologists still argue about prostate cancer, but now we have BPH to worry about as well. In the early 1980s, a patient seen at our institution with symptoms of prostatism underwent a standard workup consisting of a careful history and physical examination, urinary flow rate, postvoiding residual determination by catheterization, cystoscopy, intravenous pyelogram to rule out upper tract disease, measurement of the serum urea nitrogen and creatinine levels, and urinalysis. Once the diagnosis of BPH had been established, there were only three options for treatment. These included "watchful waiting," a Foley catheter, or prostatectomy, usually by transurethral resection. Patients opting for prostatectomy seemed satisfied with the results, and the morbidity and mortality seemed to be low. In the later part of the 1980s, however, a number of studies were published which suggested that the long-term mortality of TURP was higher than that of open prostatectomy because of an excess of cardiovascular deaths.[6] Further, the reoperative rate of 2% per year[6] and the overall complication rate of 18% were higher than expected.[7] The long-term mortality risk was ultimately debunked by a study which showed that when existing comorbidities were accounted for at the time of the operation, there were no differences in long-term mortality risk ratios.[8] Data such as these, however, coupled with the medicoeconomic effects of the procedure, fueled efforts to introduce alternatives to TURP including the use of pharmacotherapy.

On February 8, 1994, the Agency for Health Care Policy and Research under the US Department of Health and Human Services issued practice guidelines for the diagnosis and treatment of BPH.[9] For patients presenting with symptoms of prostatism in the 1990s, in addition to a detailed medical history and physical examination, the cornerstone of the diagnostic evaluation is a quantitative symptom assessment using the thoroughly validated American Urological Association Symptom Score, which is identical to the International Prostate Symptom Score (IPSS) discussed by Narayan and Indudhara.[1] This symptom index allows symptoms to be stratified as mild (score = 0 to 7), moderate (score = 8 to 19), or severe (score = 20 to 35). Patients with mild symptoms are not recommended to have treatment other than watchful waiting. Patients with moderate symptoms compose the largest subgroup and more frequently select pharmacologic therapy. Although patients with severe symptoms more often select surgical therapy, there is still considerable overlap with medical therapy as an initial choice for these patients. Finally, in this era of alternative therapies, it is important not to ignore the traditional absolute indications for surgical therapy, including recurrent bouts of gross hematuria, refractory urinary retention, recurrent urinary tract infection, and azotemia proved to be caused by bladder outlet obstruction.

Because reimbursement for the treatment of the disease will ultimately be tied to the use of this symptom index, it is necessary for treating physicians to familiarize themselves with the index and to incorporate it into their day-to-day evaluation of patients with BPH. Uroflowmetry and postvoiding residual determination, which is now performed largely by ultrasonography, are considered optional tests in the 1990s. Like Narayan and Indudhara, we also obtain a prostate-specific antigen measurement on most of the patients whom we see for a BPH workup, and the guidelines allow this as an optional test.[1] Intravenous pyelography or renal ultrasonography for upper tract evaluation is not recommended unless hematuria or other findings are present to justify these tests. Cystoscopy is allowed only for surgical planning if invasive therapy has been selected.

In addition to the treatment options of the 1980s, treating physicians are now confronted with a panorama of new therapies to consider, including balloon dilation, urethral stints, microwave hyperthermia, laser prostatectomy, cryotherapy, and pharmacotherapy. Pharmacotherapy in-

ABBREVIATIONS USED IN TEXT

BPH = benign prostatic hyperplasia
FDA = US Food and Drug Administration
TURP = transurethral resection of the prostate

cludes the use of α-adrenergic blockers or antiandrogens, particularly 5α-reductase inhibition with finasteride. Physicians need to have some familiarity with all of these alternatives because most patients have either seen or read about these treatments in the media, often before peer-reviewed literature is available. Of the therapies evaluated by the panel that developed the federal practice guidelines, sufficient data were available to draw conclusions only for "watchful waiting," prostatectomy, balloon dilation, α-blockade, and finasteride therapy. An exhaustive meta-analysis of treatment outcomes showed that the 90% confidence interval for the chances of improvement with TURP (94% to 99%) were better than that for nonsurgical options including α-blockade (59% to 86%) or finasteride administration (54% to 78%).[9] Further, the degree of symptomatic improvement was greatest for TURP (85%) versus other therapies including α-blockade (51%) or finasteride therapy (31%).[9] The need for controlled randomized trials to evaluate the efficacy of any new therapy for BPH was highlighted in the guidelines by the fact that the median probability for symptomatic improvement was as high as 45% in patients treated with placebo, similar to the 42% figure for "watchful waiting."[9] The downside of surgical therapy is obviously the possible increased morbidity of TURP, the loss of work time due to recovery, and the need for admission to a hospital.[9] The use of laser for prostatic ablation or incision promises to improve on these factors in the future.

The old idea of dealing with the static or anatomic component of obstruction by "shrinking the prostate" is a tenet of antiandrogen therapy for BPH and addresses predominantly the epithelial component. The agent of choice because of its low incidence of side effects is the 5α-reductase inhibitor finasteride. The development of finasteride began as a study of a kindred in the Dominican Republic who had ambiguous genitalia and underdeveloped prostates.[10] They became virilized at puberty, and BPH never developed. Ultimately this disorder was linked to a deficiency of the enzyme 5α-reductase, which converts testosterone to dihydrotestosterone, the predominant androgen in the prostate.[11] A search for inhibitors of this enzyme led to the discovery and development of finasteride, which has US Food and Drug Administration (FDA) approval for the treatment of BPH. Because this drug preserved serum levels of testosterone, impotence occurred in a small percentage (3%) of patients. True to form, the drug in 5-mg daily doses "shrinks" the epithelial component of the prostate, and prostatic size decreases substantially in most patients, but this has translated to symptomatic improvement in only about a third of patients.[12] These results are similar to those for other antiandrogen therapies for BPH, including the classic study by White in 1895 documenting a 25% response rate in patients undergoing bilateral orchiectomy for BPH treatment.[13] Other problems with the drug include its slow onset of symptomatic improvement, which may take as long as six months, and a predictable decrease in serum prostate-specific antigen levels.[12]

A new idea pioneered by Marco Caine, MD, in early work on the use of α-adrenergic blockade for the treatment of BPH, was that smooth muscle in the stroma of the prostate produced a dynamic component of obstruction.[14] This concept has been validated, and several selective α_1-blockers are available for use, with differences attributed to dosing intervals, cost, and initial side effects rather than any real differences in effect. Terazosin has been the most widely studied of these drugs and has FDA approval for the treatment of BPH. These drugs must be titrated slowly to 5 or 10 mg to avoid side effects of dizziness and postural hypotension. The medication is taken at bedtime, and the symptomatic improvement is noted within days. As Narayan and Indudhara mention, studies with the combination of α-blockade and finasteride are currently in progress.[1]

A number of issues remain unresolved for the role of TURP and pharmacotherapy in the management of BPH. First, the assumption that the cost of treatment will be less may not hold if medical therapy ultimately only prolongs the interval to TURP. Figuring total average charges for prostatectomy in the United States at $11,670 in 1990 and the cost of terazosin hydrochloride ($1.00 per day) and finasteride ($1.75 per day), break-even values are obtained at 31 and 18 years, respectively. This simplistic analysis, however, ignores added physician visits, urinary flow tests, and other charges that might make these numbers less attractive.[5] Will long-term compliance or as-yet-unrecognized long-term side effects limit the usefulness of pharmacotherapy? Although the use of chip cameras has shortened the learning curve for endoscopic procedures, will urologists trained in the next decade do an adequate number of TURP procedures during their training, or will the procedure be supplanted entirely by laser or other technologies? Will medical therapies fade, leaving the next decade of BPH management to look more like the last? If the next decade changes as much as the last, perhaps we will once again have a consensus about the management of this disease.

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How to Capture a Revolution

WHAT IS IT LIKE to try to capture the flavor and meaning of a revolution while you are in the middle of it? That is what Neil W. Toribara, MD, PhD, has tried to do in the medical staff conference, "Colorectal Cancer—A New Look at an Old Problem," elsewhere in this issue.[1] The understanding of colorectal carcinogenesis is rapidly being transformed by a multifaceted revolution in genetics and cellular biochemistry. The title of Toribara's review could just as easily have been "Colorectal Cancer—The New Look of an Old Problem" because this scientific revolution has converted the concept of colonic carcinogenesis from a relatively simple, multistep, histologic progression (the adenoma-carcinoma sequence) to a multidimensional process with histologic, biologic, genetic, and biochemical components.

The conceptual advances in the genetics and cellular biochemistry of colonic carcinogenesis have important clinical meaning for the prevention, early detection, and treatment of human colorectal cancer. Revolutions pose new challenges for all involved, and this one is no exception. The challenge for basic science and clinical investigators is to define the clinically useful components of the genetic and biochemical understanding of colonic carcinogenesis. The challenge for clinicians is to incorporate the useful concepts into the care of patients with or at risk for colorectal cancer.

As reviewed (and referenced) by Toribara,[1] several specific acquired genetic events—activation of the K-*ras* oncogene, inactivation of the putative tumor suppressor genes, *APC* ("adenomatous polyposis coli"), *DCC* ("deleted in colorectal cancer"), *P53*, and *hMSH2*—have become accepted as relevant to the process of colonic carcinogenesis. Exciting as these genetic discoveries are, they are only the beginning of the story. The depth of understanding of the cellular and biochemical consequences of these genetic alterations and the speed at which this field is advancing may not be as widely recognized.

Activation of the K-*ras* oncogene is a good example of the first point (depth of understanding). The normal K-*ras* gene codes for a 21-kd guanosine triphosphate (GTP)-binding protein called p21 that is critically positioned on the inner surface of the plasma membrane to function in transducing signals from the cell surface to intracellular targets. This protein is anchored to the plasma membrane by a lipid (farnesyl) intermediate that is added after translation. The biochemical details of at least one K-*ras*-dependent pathway have been recently described.[2] A simplistic description of the pathway is that epidermal growth factor binding to the transmembrane epidermal growth factor receptor results in tyrosine autophosphorylation of the cytosolic tail of the receptor. This tyrosine phosphorylation results in an interaction between two cytosolic proteins, GRB2 and SOS. The complex facilitates the release of guanosine diphosphate (GDP) from p21 (the K-*ras* gene product) and allows GTP to bind to p21. This GTP binding activates P21, and the activation initiates an intracellular kinase cascade (raf1, methylamino-purine [MAP] kinase kinase, MAP kinase) that ultimately results in transcriptional regulation. The normal p21 also has a guanosine triphosphatase (GTPase) activity that hydrolyzes bound GTP to GDP and inactivates p21, thus turning off the signal transduction pathway. Thus, the normal p21 plays a central role as an on-off switch (activation by GTP, inactivation by GTP hydrolysis) in regulating signal transduction. Mutations in K-*ras* occur in about 50% of colonic adenomas and carcinomas. The mutations are almost always point mutations in codons 12, 13, or 61 of the gene. These mutations result in a loss of the GTPase activity of p21, thus preventing inactivation of the signal transduction pathway. Cells with mutated K-*ras* can be viewed as having a constitutively activated signal transduction system. It is easy to imagine how constitutive activation of some signal transduction systems (growth factor systems) could result in a clone of cells with a growth advantage.

The detailed understanding of the biochemical consequences of K-*ras* mutations provides the basis for interventions to block the abnormality. At least two inhibitors of the farnesyl transferase that is required to properly anchor p21 to the plasma membrane have been developed and are being tested as chemopreventive or treatment agents in cell culture and animal systems.[3]

Although not all of the oncogene and tumor suppressor gene products are as precisely characterized as p21, a great deal is known about many of them, and the field is moving rapidly. The known functions of the genes frequently mutated in colon cancer are listed in Table 1. The common pattern of progress in this field is that the finding of genetic abnormalities in colonic cancers and adenomas led to the identification of the specific gene(s) involved, which allowed the identification and characterization of the relevant gene product. In some cases the precise function(s) of the gene products has been determined. It seems

ABBREVIATIONS USED IN TEXT

FAP = familial adenomatous polyposis
GDP = guanosine diphosphate
GTP = guanosine triphosphate
GTPase = guanosine triphosphatase
HNPCC = hereditary nonpolyposis colorectal cancer
MAP = methylaminopurine

likely that those findings will lead to biochemical (peptides or nucleotides) approaches to block carcinogenesis before direct genetic interventions become feasible.

The dramatic increase in the speed of the genetic and biochemical understanding of colonic carcinogenesis can be illustrated by the two strong familial colon cancer syndromes: familial adenomatous polyposis (FAP) and the hereditary nonpolyposis colorectal cancer (HNPCC) syndromes. Familial adenomatous polyposis was originally described in 1970 as a syndrome characterized by the development of thousands of adenomas.[4] Genetic linkage studies initially identified the location of the gene on chromosome 5 in 1987.[1] The *APC* gene was identified in 1991, and the precise gene function is being actively investigated (see Table 1). This seemed like rapid progress as it developed, but the pace of the HNPCC story has been stunning.

The initial HNPCC family was described in 1895 and "revisited" in 1971.[5] The HNPCC syndromes are characterized by the autosomal dominant inheritance of a gene that produces cancers of the colon and, in some families, other sites (endometrial, ovarian, gastric, brain). The colon cancers in these families tend to occur earlier than typical colon cancer (mean age 42), are often multiple, and occur predominantly (75%) in the proximal colon. A genetic locus responsible for some HNPCC families was reported in May 1993, and the chromosome 2 gene responsible for HNPCC (*hMSH2*) was reported in December 1993 (see Toribara for references[1]). A second genetic locus on chromosome 3 was linked to some HNPCC families in November 1993,[6] and the identification of the relevant gene (*hMLH1*) was reported in March 1994.[7] Germ-line mutations in the *hMSH2* and *hMLH1* genes are thought to be responsible for at least 50% of HNPCC families.

How can two distinct genetic defects lead to the same clinical syndrome? The two genes code for proteins that together are critical to the maintenance of integrity of the genome. The *hMSH2* gene is thought to identify and bind to mismatched base pairs that occur during DNA replication. The *hMLH1* gene is thought to bind to *hMSH2* and to coordinate the action of the enzymes that repair the mismatched DNA. The loss of function of either of these two gene products could easily result in a failure of point mutation repair and a markedly increased rate of mutation (genomic instability). In less than a year, we have progressed from knowing almost nothing about the genetic loci responsible for HNPCC to knowing the genetic sites, the genes involved, and their function—a remarkable pace!

Revolutions lead to challenges for both the participants and the rest of society. There is, in my view, a critical challenge for clinical investigations to keep pace with the advances in the basic understanding of colonic carcinogenesis. Classic types of clinical investigations of colorectal cancer have made substantial recent advances (see Toribara for references[1]). Epidemiologic and clinical studies have shown that a positive family history is an important risk factor for colonic adenomas and carcinomas and that this is likely due to the inheritance of susceptibility genes. Controlled prospective and case-control studies have for the first time demonstrated the effectiveness of screening with fecal occult blood tests and sigmoidoscopy. Controlled trials of the effectiveness of polypectomy in preventing colon cancer death and chemoprevention trials have demonstrated a dramatic regression of adenomas in

TABLE 1.—*Genes Frequently Mutated in Colon Cancer*

Gene	*Function of Gene Product*
K-*ras*	GTP binding protein; regulates signal transduction from cell surface receptors to intracellular targets; mutations lead to a constitutive activation of signal
APC	Germ-line mutation in familial adenomatous polyposis and Gardner's syndrome; interacts with catenin; may modulate cell-cell interactions; mutations thought to lead to a loss of function
DCC	Cell-surface protein; found abundantly in goblet cells; some homology to cell adhesion molecules; may modulate cell-cell interactions; mutations thought to lead to a loss of function
P53	Nuclear phosphoprotein; transacting transcription factor; controls cell replication by regulating proteins (cyclin and cyclin-dependent kinases) that are required for progression through the cell cycle (from G1 to S phase), prevents replication of cells with damaged DNA; promotes apoptosis in some cells; mutations lead to a loss of fidelity of DNA replication (genomic instability)
hMSH2	Germ-line mutation in some families with hereditary nonpolyposis colorectal cancer (HNPCC); recognizes mismatched nucleotides in DNA and initiates their repair; mutations lead to a rapid accumulation of genetic errors (genomic instability)
hMLH1	Germ line mutation in some families with HNPCC; probably binds to *hMSH2* and mediates the repair of mismatched nucleotides; mutations lead to rapid accumulation of genetic errors (genomic instability)

patients with familial polyposis after treatment with the nonsteroidal anti-inflammatory drug sulindac, although the mechanism of the effect is not yet known. Treatment trials have shown a benefit (albeit modest) for adjuvant therapy with fluorouracil and levamisole hydrochloride in Dukes' stage C colon cancer and with the combination of radiation therapy and chemotherapy in Dukes' stage B2 and C rectal cancer.[8] Chemoprevention trials have recently been launched to test the effectiveness of interventions—low-fat, high fruit and vegetable diet; fiber supplementation; nonsteroidal anti-inflammatory drugs; calcium; antioxidants—in the prevention of sporadic adenoma recurrence.

These are important advances, and their importance should not be understated, but a great deal more needs to be done. We now have an opportunity and a need to translate the basic science revolution into clinical practice. The potential effect of the new genetic and biochemical understanding of colonic carcinogenesis is broad, ranging from risk stratification, screening, and early detection to chemoprevention and treatment. It is now possible in most FAP families to use a blood test[1] to determine if a person has inherited the mutant *APC* gene and will have the clinical syndrome. The medical and ethical consequences of genetic diagnosis need to be evaluated. Do preventive measures instituted early affect the natural history of FAP? What is the optimal screening protocol for known gene carriers? What are the psychosocial and medicolegal consequences of a genetic diagnosis of FAP? Are there other genetic influences that alter the phenotype? What is the cellular function(s) that is (are) lost by mutation of the *APC* gene, and can it be biochemically or genetically restored to the cell?

A blood test capable of detecting gene carriers in at least some HNPCC families is expected to be commercially available soon. This will generate a series of important research questions comparable to those listed for FAP. Are more subtle alterations in the *APC* or *hMSH2* or *hMLH1* genes (or other definable genes) responsible for the familial predisposition to "sporadic" colorectal cancer?

We need to know if detecting the acquired genetic alterations that occur during carcinogenesis in stool, colonic lavage fluid, or randomly obtained biopsies can identify high-risk groups. Can rational preventive or treatment strategies based on the genetic and biochemical knowledge of colonic carcinogenesis be developed and clinically tested?

The number of interesting questions raised by this ongoing revolution seems endless. Clinical investigators need to help identify the most important questions and collaborate with the basic scientists to answer them. Basic scientists need to help find ways to apply their basic tools and assays to large clinical populations, and institutions must recognize the obstacles to this type of translational research and support mechanisms to facilitate it. Practicing clinicians will need to be aware of and support ongoing clinical trials; we will all need to understand and promptly take advantage of the clinically useful results of such trials. Finally, there is a major educational challenge for all of us because of the rapid expansion of the knowledge base. THE WESTERN JOURNAL OF MEDICINE can play an important role for its readers in this area.

Victor Hugo wrote, "Would you realize what revolution is, call it progress; and would you realize what progress is, call it tomorrow." I can hardly wait until tomorrow.

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The Acquired Immunodeficiency Syndrome in Older Persons

To the Editor: Since it was first reported 13 years ago, the acquired immunodeficiency syndrome (AIDS) has emerged as a leading cause of death in young and middle-aged persons. This has led to the mistaken impression among some health care professionals and the general public that AIDS is not a health issue for older persons when, in fact, it is being increasingly diagnosed in persons older than 50 years.[1,2]

During the first decade of the human immunodeficiency virus (HIV) epidemic in the United States, about 10% of AIDS cases were in persons 50 years of age or older, accounting for more than 20,000 cases to date. After 1989, about 30% of older persons diagnosed with AIDS have been older than 60, and relatively more of these cases have been among women and whites.

The relative distribution of risk factors for acquiring HIV disease is different for older persons. Homosexuality and injection drug use account for 90% of cases of AIDS in persons 13 to 49 years old, but these have been the primary risk factors in only 20% of cases in persons older than 70.[1] In older persons, transfusion with blood or blood products has been the most frequent means of being infected with HIV. Although the risk of acquiring HIV infection from transfusions diminished after widespread blood screening for the virus was implemented in 1985, a small but finite risk—estimated to be 1 in 250,000 units in 1993—still exists.[1,3]

Of Americans older than 50 years, 10% report at least one risk factor for HIV infection. The most common are a history of multiple sexual partners, sexual encounters with high-risk partners, especially for the estimated 1 million homosexuals older than 65, and a history of transfusion. Of AIDS cases among older persons, 10% are attributed to heterosexual transmission, which is the highest percentage in any age group. This rate seems to be increasing.

Many older persons with HIV infection resulting directly or indirectly from blood transfusion have not been tested and do not know of their potential infectivity. Among older persons with at least one risk factor for HIV, 90% have not undergone serologic testing.[4] When controlled for other demographic variables, the population of older persons with risk factors for HIV is a fifth as likely to undergo HIV testing as persons 20 to 29 years of age. In view of this relative paucity of testing in older persons, it should not be surprising that older people use condoms much less frequently—reported to be a sixth that of persons aged 20 to 29 years.[4] This is ironic because older gay and bisexual persons have been reported to be more compliant in practicing safe sex than younger at-risk persons.

The clinical presentation of AIDS-HIV disease in older persons is different.[1,2,5] Published reports support the clinical impression that HIV disease progresses more rapidly in older persons—both from asymptomatic infection to overt immunocompromise and from full-blown AIDS to death. The number of cases of AIDS diagnosed in the same month as death occurs increases with age and is most pronounced in persons older than 70.[1] A contributing factor is a delay in diagnosis, which may result from a low index of suspicion of HIV infection by both patients and their physicians, as well as the increased frequency with which nonspecific signs such as weight loss, fatigue, and deteriorating mental and physical function herald the onset of disease in older persons.[1,3] Although *Pneumocystis carinii* pneumonia is the most common opportunistic infection seen in HIV-infected adults, AIDS-related dementia or encephalopathy is commonly a first sign of the disease in the elderly.

Physicians should recognize that sex occurs among their older patients and discuss safe sexual practices with them. Older patients may be more reluctant to volunteer this information, so clinicians need to be adept at soliciting it. They also must be attuned to relevant nuances in the prevention message, such as the older woman's potentially increased risk of age-related vaginal trauma and, therefore, transmission by heterosexual contact.

Recognizing risk factors and early signs of HIV disease in older persons presents special challenges to clinicians, but is critical to preventing the spread of the disease and to delaying secondary complications in seropositive patients. Clinicians also need to be aware of potential side effects of drugs, iatrogenic complications, and the need to tailor treatment for older AIDS patients. This will be challenging as AIDS care is increasingly provided in outpatient and community-based settings.

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A Patient's Choice?

To the Editor: The "Lessons From the Practice" by Theodore Schwartz, MD, in the July issue[1] was touching and humbling. I think it particularly notable that the event took place in the mid-1960s. If this episode were to take place in the 1990s, the story would have ended differently—probably in front of a jury. Nowadays, physicians are damned if they do *not*—inform, caution, warn, educate exhaustively, and record it—or damned if they do all of these. I say "damned if they do" because the written,

recorded verification of informed consent is sure to be either ignored or attacked. In the final analysis, a huge monetary award would be made on the basis of sympathy for the unfortunate woman who lost both her sight and her child, notwithstanding the fact that she assumed responsibility by exercising her informed "right to choose." Oh, for the good old days!

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* * *

Dr Schwartz Responds

To the Editor: I agree with Dr Taylor that in terms of malpractice litigation, those were, indeed, the good old days. Back then, the notion that I might be sued never entered my mind, and I am certain that the idea of a suit never occurred to my patient, either. We shared an intimacy born of a mutual trust that could not have been easily shaken.

Whether such a relationship as we shared could today withstand the lure of a big money settlement is problematic. Certainly, the chances of avoiding litigation are better for an endocrinologist in Boise than for a plastic surgeon in San Diego. We should be mindful, though, that the past 30 years have seen much more than an increase in malpractice settlements. A lawsuit might well be avoided today because the chance that my patient's course would have such a shattering outcome is far less likely. Improvements in treating a pregnant woman with diabetes and diabetic retinopathy have reduced the attendant risks dramatically. Furthermore, the prospect of a therapeutic abortion may no longer seem appalling to many American women, including some Catholics.

Finally, I remind Dr Taylor of the countless patients he and I have seen over the years, patients who were honest, trusting, and grateful for our efforts. While our glass is no longer brimming over, it remains nearly full.

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The Beef About Balance

To the Editor: Wouldn't it be wonderful if eating only vegetables could lead to better health? In "Health Effects and Prevalence of Vegetarianism" in the May 1994 issue,[1] White and Frank have reviewed current literature on the health benefits of vegetables, and the authors' message is an unequivocal "yes." Despite some issues of vitamins and minerals, vegans do quite well in achieving appropriate nutritional goals. In addition, vegetarians seem to have lower risks for heart disease, gallstones, hypertension, and obesity.

The problem is the science. Proving that the vegetarian diet alone is responsible for such claims is not easy. Many variables need controlling: exercise, stress, smoking, alcohol consumption, genetics, and age, for example. Investigators have had a hard time separating these variables out to draw firm conclusions.

Being a true vegetarian is really a personal statement because the overwhelming majority of humans are either partial vegans—lacto- or lacto-ovo vegetarians—or omnivores. More common is the trend to eat more vegetables, fruit, grains, fish, and poultry; animal fat, excessive beef, and red meat are either avoided or limited. Which diet is best in the face of so many options?

By nature humans are omnivores, allowing adaptation to environments of hunting and gathering or agriculture. The choice of a completely vegetarian diet in the face of all the available tempting dietary choices in our culture requires a substantial commitment for ethical, religious, or other personal reasons. It is therefore not surprising that vegetarians believe in vegetarianism, and the national prevalence is 1% to 2%. It is also the reason, as shown in the Stanford Five-City Project, that most vegetarians are only partial. It also raises the issue that a vegetarian diet may be a marker of other variables such as a health-conscious personality and lifestyle. The natural conceptual ramification is that a vegetarian diet should be chosen over all others because it makes you healthier.

The authors are to be congratulated for their emphasis on the positive effects of diet on one's health. The predominant conclusion from numerous epidemiologic studies is that a lower intake of dietary cholesterol and unsaturated animal fat will help prevent arteriosclerosis. That does not mean that total exclusion of animal products from the diet is healthy, particularly in infants, pregnant women, the elderly, and the ill. Such persons are at an even greater risk of the consequences of deficiencies inherent in a vegan diet: rickets, megaloblastic anemia, osteoporosis, and neuropathies occur when the diet is not carefully monitored. Most of the studies referenced do not sufficiently account for these risks because predominantly healthy adults were studied. Education is important to the success of a vegan diet.

The true value in this article is recognizing the need to better determine what is the best diet. The answer will require more research into the contribution of diet to the various diseases we wish to prevent. From a purely biologic standpoint, some animal products in the diet are not only physiologically desirable, but an efficient source of completing the daily nutritional requirements. Moderate amounts of lean red meat, poultry, and fish provide the healthy balance for vegetarians that fiber, fruit, and vegetables do for the omnivore. Your parents were right to insist that you eat your veggies . . . but just how much? The answer lies in further research into the basic biochemical science of nutrition and disease, with quality epidemiologic studies to provide us with the truth about which balanced diet is really the healthiest.

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To the Editor: The article by White and Frank on aspects of a vegetarian diet is a thorough review of much of the positive side in vegetarianism, but it fails to address much of the negative side.[1,2] Medical evidence indicates that a vegetarian diet poses a risk for young women, especially active women and athletes.

Numerous reports point out that women who fail to eat meat have a higher level of amenorrhea than their counterparts who eat meat.[3-7] Athletic amenorrhea is known to lead to premature osteoporosis.[8] Amenorrheic women who are active in competitive and recreational sports have a greater risk of injury than women who menstruate normally.[9] Eating red meat can be a part of the solution to athletic amenorrhea.[4,10]

As a psychiatrist, Dr White will appreciate the research by Gadpaille and co-workers, who suggest a link between athletic amenorrhea in runners and major affective disorders and eating disorders.[11] Of 13 amenorrheic runners studied, 12 (87%) were vegetarians. In this group with amenorrhea, 8 (62%) had diagnosable eating disorders and 3 (23%) had a major affective disorder. In 19 runners who were menstruating, there were only 3 (15%) vegetarians, no eating disorders, and no major affective disorders. Other psychiatric specialists caution against the overenthusiastic advocacy of a low-fat, meatless "healthy lifestyle" in vulnerable, adolescent girls.[12]

Although White and Frank's article did discuss minerals, it certainly glossed over the issue of iron in vegetarianism. I reported at the American College of Sports Medicine meeting of 1993 that a third of teenaged cross-country runners were iron deficient, as judged by serum ferritin levels.[13] Those runners with low serum ferritin levels had an injury rate twice that of runners with serum ferritin levels of more than 24 μg per liter (24 ng per ml). Because iron deficiency is the leading nutritional deficit in this country, to encourage a diet that further contributes to iron deficiency makes little sense. Other consequences of iron deficiency were recently reviewed in this journal.[14]

Although the reviews cited state that a plant-based diet improves longevity, these studies are, in fact, somewhat equivocal.[15,16] Female Seventh-Day Adventists who eat meat and strict vegetarian Adventists had no difference in their mortality rates.[15] While males eating meat four to seven days a week had a 1.5 risk of increased mortality, the number for those eating meat one to three days per week was much smaller, and statistical significance was not reported.

In the large study quoted, there was no difference in all-cause mortality in Seventh-Day Adventists who ate foods low in fat, little cheese and eggs, no meat or milk, and those who did not trim fat, ate cheese and eggs at least three days a week, and had milk or meat more than one day a week.[15]

In a study of 11,000 customers of health food shops, there was no difference in all-cause mortality between vegetarians and nonvegetarians.[17] A survey of diet and lifestyle determinants of mortality among German vegetarians revealed that vegetarians who occasionally ate meat had a significantly lower mortality than those who were strict vegetarians.[18] Even the recently advocated life-prolonging Mediterranean diet includes meat, chicken, and fish.

There are now an estimated 1.5 million adolescent competitive female athletes in the United States and more female athletes between ages 18 and 25 years. Although it is appropriate to review the vegetarian lifestyle, to substitute an espousal of vegetarian values for a balanced scientific article does patients and the medical community an injustice. It seems inappropriate for young women to sacrifice their bones, become anemic, develop eating disorders, and have injuries because they are "ecosensitive." We would never allow this to happen to our young men. First do no harm!

Nutrition "perfectionism" based on low-fat diets, animal rights, and ecosensitive issues and manifested by vegetarianism in young women must be countered with nutritional moderation. It seems preferable to eat meat, chicken, or fish on a daily basis, have a low fat intake, and, in fact, have a healthier lifestyle than the strict vegetarian.

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To the Editor: I was most interested in the article by White and Frank on vegetarianism, particularly in their statement that vegetarians have lower mortality than the population at large. I would have thought that the lifetime incidence of mortality among vegetarians was the same as among the omnivorous, that is, 100%. If it is true that vegetarians do not die, I think this finding is much more significant than is evidenced by the small print in which this remarkable result was presented. Perhaps the statement that they have a lower mortality than other people was somewhat misrepresentational. If they do die, of what do they die and when?

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* * *

Drs White and Frank Respond

To the Editor: Successful veganism requires a commitment and a modest sophistication in food choices, as Berquist and Ceresa and we in our article acknowledge. Eating animal-derived foods, in contrast, seems widespread and natural among humans.[1] Because meat was, for our ancestors, a scarce but rich source of protein, it was highly desired. This remains true, except that meat has become abundant. With a fast-food outlet on each corner, successful "hunting" has acquired long-term dangers. Beef supplied by the modern meat-producing industry, marbled with saturated fat, does not resemble wild game in its fat composition—although fish and chicken do. While we concur that modest consumption of lean meat is probably compatible with good health, we contend that humans do not need and may be harmed by frequent meat consumption—depending upon the fat composition. Beans, however, are a good source of protein and a poor source of fat and cholesterol.

One statement made by Berquist and Ceresa requires correction. The participants in the Stanford Five-City Project ate either a vegan or a low-fat lacto-ovo vegetarian diet. No conclusion that "the majority of vegetarians are only partial" is justified, for we do not know the proportion of subjects in each group. We, too, await high-quality epidemiologic data for the answer to this and other questions. In the meantime, we doubt that many could reject our conclusion that everyone could benefit, physiologically or ecologically, from reduced meat consumption.

Dr Loosli has made a clinically important point, to which we briefly alluded: vegetarianism may be associated with eating disorders, hyperathleticism, anemia, and menstrual irregularity in young women. Whether the meat restriction is causal or merely an associated feature remains undetermined. Decreased meat consumption can be associated with lower circulating estrogen levels in women, as documented by Pedersen and colleagues, who speculate that increased fiber or phytoestrogen intake, or both, may be the cause.[2] They also speculate that such a diet may protect against breast cancer and may decrease reproductive capacity, but the latter notion is partially contradicted by the vegetarians taking part in the study having, on average, a greater number of children than their omnivorous counterparts.

An alternative explanation of amenorrhea in vegetarian, obsessive runners, such as those studied by Gadpaille and co-workers, is that such athleticism is an eating-disorder equivalent.[3] Vegetarianism would be a rationalization for dietary restrictions and amenorrhea a symptom of the underlying disorder—as it is in anorexia nervosa.

Clinical experience and some data suggest that certain young women restrict their diets and call themselves vegetarians, but their motives are more psychopathologic than environmental or salubrious. They are at increased risk for iron-deficiency anemia.[4,5]

Our review was intended to inform physicians about vegetarian diets and the issues they should consider in a clinical setting. Dr Loosli makes it clear that in young women, a menstrual history is important, especially in athletes, as is a complete blood count in selected patients. Consultation with a nutritionist may help some patients. The conclusion, however, that all young vegetarian women will "sacrifice their bones, become anemic, develop eating disorders, and have injuries" is hyperbole, unsubstantiated by the available literature. In general, the literature concludes that vegetarians derive health benefits from their dietary choices.

Finally, Dr Fitzgerald correctly points out an error in our highlights section. While it would certainly be worth highlighting if vegetarians had lower mortality than omnivores, we regret that it is only true that they have lower mortality rates than do omnivores.

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Lessons From the Practice

'He Who Saves a Life Saves a Universe'*

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I met Marcel when I was a Peace Corps volunteer in the West African republic of Cameroon. He was the only physician for the 25,000 people in the district. We lived in Nguelemendouka, the district seat and a village of about 3,000 people. On rainy days when the roads were not passable, I spent a fair amount of time just hanging around the hospital watching Marcel at work.

Marcel was from a tribe that was not "politically correct." They were Christians and from western Cameroon; those in power were Moslems and from northern Cameroon. His father had spent more than a decade in prison for being a member of one of the outlawed opposition parties and had died a broken man shortly after being released. Despite obstacles, Marcel had won admission to Cameroon's medical school. The school was quite good, with the well-equipped National Hospital as its teaching hospital. After graduation Marcel, like his classmates, paid for his education with government service and was sent to one of the district hospitals as the local health officer.

Marcel was serious about his work and often expressed frustration at the difficulties he faced in his practice of medicine. There were limited resources, and his patients often came to him too late to be helped. The hospital had no electricity or running water. The patients' families were responsible for their relatives' food, and there was filth everywhere—mud in the rainy season and, in the dry season, dust.

Marcel had his fun-loving, relaxed side, however. He loved American country music. After Cameroonian *makossa*, his favorite tape was *Jim Reeves' Greatest Hits*. I remember a party at his house where he danced around the living room to "Bimbo." At the end of the day, we would sit and talk over our work, world affairs, or the fate of the Cameroonian national soccer team in the World Cup.

One afternoon a woman came in from one of the outlying villages. She had been in labor for two days and still no baby. This was the first time in her life that she had seen a physician. Marcel palpated the fetus and thought that it was in a transverse position. We took her to the operating room for a cesarean section.

The operating room was, by any standard, primitive and filthy. The autoclave was wood-fired. Surgical gloves were washed and reused. The open windows lacked screens, and flies buzzed around the rooms. The only anesthesia available was spinal, so our time was limited.

Marcel gave the anesthesia and began the surgical procedure. The reason that labor had not progressed was soon apparent—the pregnancy was an abdominal ectopic, with the fetus fully developed outside the uterus but stillborn. By now bleeding was profuse. Marcel was frantically trying to find the bleeding vessels and tie them off—with no electricity, so no cautery. Meanwhile, the spinal anesthesia was beginning to wear off, and I was holding the patient's shoulders down as she tried to jump off the table. To this day, I tremble when I recall her cries from the pain and for her baby. Finally, Marcel closed her abdomen.

All through this horrific time, the nurse was calling out the patient's falling blood pressure. I do not know how much blood she had lost, but clearly she needed a transfusion. The nearest blood bank was in the capital, six hours away by road if it did not rain. Marcel had no blood-typing sera, either. That is when he did something that is still the finest and noblest act I have ever seen.

"I'm O-negative," he said. And as he gave the patient his own blood, her pressure stopped falling. Her condition stabilized, and she survived to leave the hospital.

Since then, Marcel has been to Paris for more training in pediatrics. I got a letter from him last week. He has been promoted and is now Chief of Pediatrics at the Provincial Hospital in Bertoua in eastern Cameroon. Things are difficult in Cameroon these days—prices for its major exports, oil, coffee, and cocoa, have fallen dramatically. There are boycotts and disagreements between the government and the opposition. But Marcel still tries, and he still cares.

**The Babylonian Talmud*, Tractate Sanhedrin, Folio 37, Soncino Press, London, England, 1987.

(Sloan VS: 'He who saves a life saves a universe.' West J Med 1994; 161:530)

At the time this commentary was written, Dr Sloan was a Fellow in rheumatology at the University of California, San Francisco, School of Medicine. He is currently a Fellow in rheumatology at the Robert Wood Johnson Medical School, New Brunswick, New Jersey.

Reprints are not available. Address correspondence to Victor S. Sloan, MD, One Robert Wood Johnson Place, MEB484, New Brunswick, NJ 08903.

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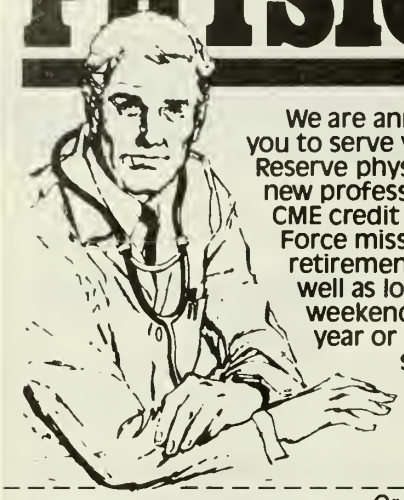

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† Latest available annual data: January to December 1991.

‡ *In vitro* susceptibility does not necessarily imply *in vivo* efficacy.

Please see brief summary of prescribing information for contraindications, warnings, precautions and adverse reactions on adjacent page.

References: 1. Neu HC, Wilson APR, Grüneberg RN: Amoxicillin/clavulanic acid — a review of its efficacy in over 38,500 patients from 1979 to 1992. *J Chemother* 1993;5(2):67-93. **2.** Data on file, SmithKline Beecham Pharmaceuticals. **3.** Data from the Institutes for Microbiology Research, Franklin, Tenn. **4.** Neu HC: Contribution of beta-lactamases to bacterial resistance and mechanisms to inhibit beta-lactamases. *Am J Med* 1985;79(suppl 5B):2-12.

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Bacteriological studies to determine the causative organisms and their susceptibility to *Augmentin* should be performed together with any indicated surgical procedures Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above Once results are known, adjust therapy, if appropriate

Contraindications: Patients with a history of allergic reactions to any penicillin, or patients with a history of *Augmentin*-associated cholestatic jaundice/hepatic dysfunction.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS BEFORE INITIATING THERAPY WITH *AUGMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.** Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis" After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C difficile* colitis Use *Augmentin* cautiously in patients with evidence of hepatic dysfunction Hepatic toxicity associated with *Augmentin* use is usually reversible On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide) These have generally been cases associated with serious underlying diseases or concomitant medications (see CONTRAINDICATIONS and ADVERSE REACTIONS–*Liver*)

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients There are no data with *Augmentin* and allopurinol administered concurrently

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin* There are, however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman

Adverse Reactions: *Augmentin* is generally well tolerated The majority of side effects observed in clinical trials were mild and transient, <3% of patients discontinued therapy because of them. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose Other less frequently reported reactions include abdominal discomfort, flatulence and headache

The following adverse reactions have been reported for ampicillin class antibiotics

Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis, mucocutaneous candidiasis and pseudomembranous colitis Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis). These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (see WARNINGS) A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications Interstitial nephritis and hematuria have been reported rarely Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin* Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely

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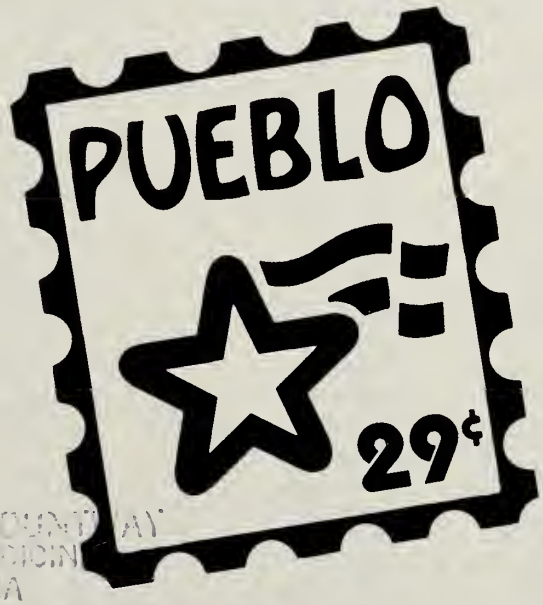

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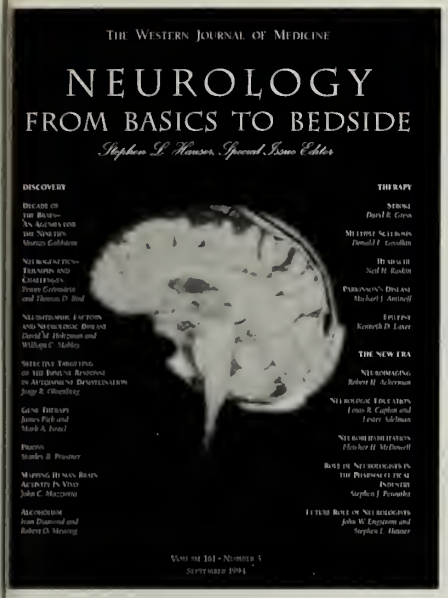

Stephen Hauser, MD
Special Issue Editor, 1994

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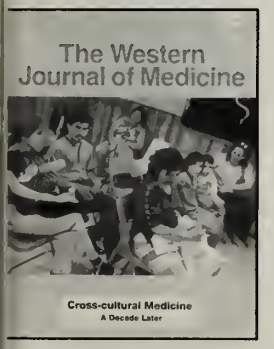

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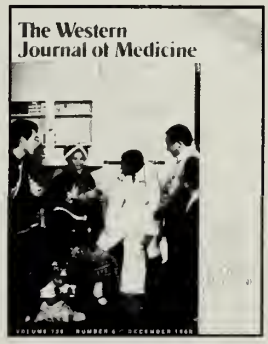

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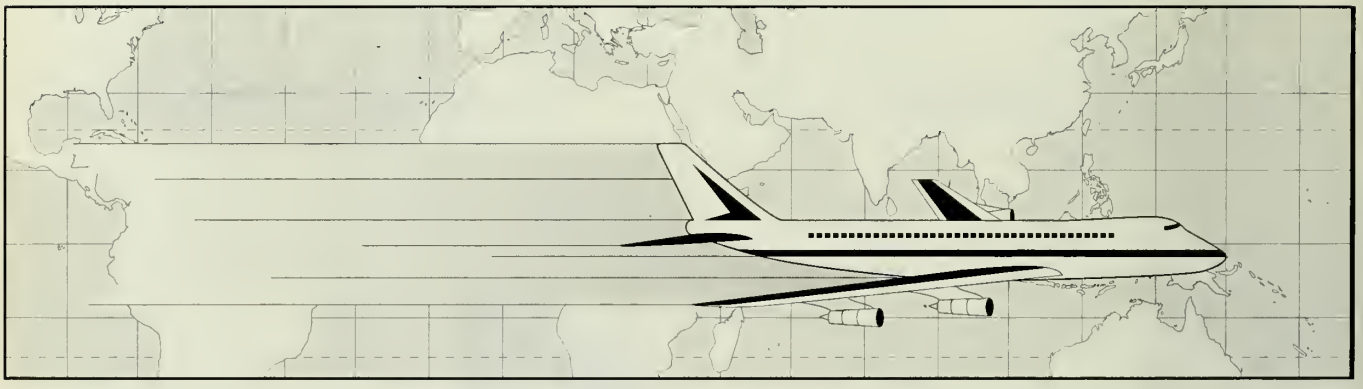

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

January 12-13—**2nd Annual Current Topics in Critical Care Medicine.** Mayo Clinic-Scottsdale at the Ritz-Carlton Hotel, Phoenix. Thurs-Fri. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 14-15—**5th Annual Current Topics in Anesthesiology.** Mayo Clinic-Scottsdale at the Ritz-Carlton Hotel, Phoenix. Sat-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 16-20—**23rd Annual Phoenix Surgical Symposium.** Maricopa Medical Center and Phoenix Surgical Society at the Phoenician Resort, Scottsdale. Mon-Fri. Contact: Beverlee Anderson, (602) 267-5366.

January 20-22—**Winter Symposium on Headache.** American Association for the Study of Headache at the Marriott's Camelback Inn, Scottsdale. Fri-Sun. Contact: (800) 845-1720.

January 20-22—**Electromyography in Clinical Practice.** Mayo Clinic-Scottsdale. Fri-Sun. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

January 25-27—**Clinical Recognition and Management of Heart Disease.** American College of Physicians and Univ of Arizona College of Medicine at University Medical Center, Tucson. Wed-Fri. Contact: (215) 351-2400, ext 2600.

February 6-10—**Psychopharmacology Review Course.** University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Mon-Fri. Contact: Lynne Mascarella, U of A.

February 12-16—**International Congress VIII on Endovascular Interventions: Breaking the Barriers.** American College of Angiology at the Phoenician Resort, Scottsdale. Sun-Thurs. Contact: (602) 266-2200.

February 16-18—**Mayo Interactive Surgical Symposium.** Mayo Clinic-Scottsdale at the Orange Tree Golf and Conference Resort, Scottsdale. Thurs-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 16-18—**18th Annual Midwinter Symposium—Advances in Obstetrics and Gynecology.** Maricopa Medical Center and Phoenix Ob/Gyn Society at Scottsdale Plaza Resort. Thurs-Sat. Contact: Beverlee Anderson, (602) 267-5366.

February 17-19—**21st Annual Scientific Meeting—Anesthesia for the '90s.** University of Arizona College of Medicine and Arizona Society of Anesthesiologists at the Wyndham Paradise Valley Resort, Scottsdale. Fri-Sun. (602) 947-5400.

February 19-22—**Practical Radiology.** University of Arizona College of Medicine at Loews Ventana Canyon Resort, Tucson. Sun-Wed. Contact: Lynne Mascarella, U of A.

February 23-24—**Hepatology Update 1995.** Mayo Clinic-Scottsdale at the Ritz-Carlton, Phoenix. Thurs-Fri. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 23-25—**21st Annual Frontiers in Ophthalmology.** St Luke's Medical Center at Red Lion's La Posada Resort, Scottsdale. Thurs-Sat. Contact: (602) 274-7479.

February 24-25—**Mayo Plastic Surgery Symposium.** Mayo Clinic-Scottsdale at the Ritz-Carlton Hotel, Phoenix. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 24-26—**1995 Scientific Assembly—American Academy of Family Practice.** The Pointe Hilton at Tapatio Cliffs, Phoenix. Fri-Sun. Contact: American Academy of Family Practice, Arizona Chapter, (602) 249-2021.

February 27-March 2—**Pediatric Update.** Phoenix Children's Hospital at Marriott's Camelback Inn, Scottsdale. Mon-Thurs. Contact: (602) 239-5783.

March 5-9—**Radiology in the Desert: Practical Aspects of Radiology and Imaging.** University of Michigan Medical School at Marriott's Camelback Inn Resort, Scottsdale. Sun-Thurs. Contact: Lynne Mascarella, U of A.

March 8-10—**Clinical Reviews 1995.** Mayo Clinic-Scottsdale at the Ritz-Carlton, Phoenix. Wed-Fri. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 11—**Frequently Encountered GYN Problems in Primary Care.** Mayo Clinic-Scottsdale at the Ritz-Carlton, Phoenix. Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 11—**Controversies in Hypertension.** Mayo Clinic-Scottsdale at the Ritz Carlton, Phoenix. Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 17-19—**19th Annual James H. McDonald Urological Seminar.** Maricopa Medical Center and Phoenix Urologic Society at Scottsdale Plaza Resort. Fri-Sun. Contact: Beverlee Anderson, (602) 267-5366.

March 30-April 1—**4th Annual Urogynecology and Disorders of the Pelvic Floor.** Mayo Clinic-Scottsdale at The Pointe Hilton Resort at Tapatio Cliffs, Phoenix. Tues-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

April 5-8—**Primary Care Update.** University of Arizona College of Medicine at the Tucson East Hilton. Wed-Sat. Contact: Lynne Mascarella, U of A.

May 6-9—**2nd Mayo Telemedicine Symposium and 2nd International Symposium on the Medical Aspects of Telemedicine.** Mayo Foundation. Sat-Tues. Contact: (800) 323-2688.

May 7-11—**Fundamental Principles of Pharmacokinetics and Toxicokinetics for the Industrial Scientist.** University of Arizona College of Medicine at the Westward Look Resort, Tucson. Sun-Thurs. Contact: Lynne Mascarella, U of A.

CONTACT INFORMATION

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ANESTHESIOLOGY

January 4-7—**Anesthesia Update.** UCSD at Hotel del Coronado, San Diego. Mon-Sat. 21 hrs. $350. Contact: UCSD.

February 3-5—**33rd Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: David Steward, MD, Director, PO Box 54700, Los Angeles 90054. (213) 669-2262.

CARDIOLOGY

January 20-22—**Clinical Nuclear Cardiology: Case Review With the Experts.** American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles. Fri-Sun. 20 hrs. Contact: American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739

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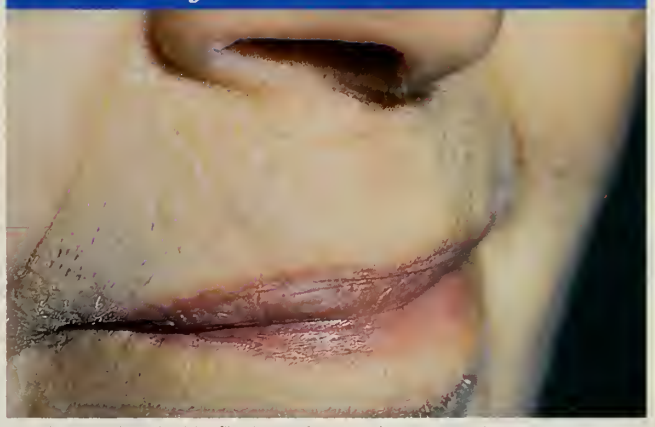
Which Therapy Cured This Infection?

❑ oral cephalosporin ❑ oral erythromycin ❑ topical mupirocin

Pretreatment

After 12 days' treatment



Actual unretouched physician file photos of 71-year-old patient with impetigo

Presentation:
Classic erythematous yellow-crusted lesions

Diagnosis: Impetigo

Observations:
Resolution of infection

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Turn page for the answer.

CONTINUING MEDICAL EDUCATION

(Continued from Page 548)

April 28-30—**Arrhythmias: Interpretation, Diagnosis, and Management.** Medical Education Resources at Sheraton Desert Inn, Las Vegas. Fri-Sun. 11 hrs. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

May 11-13—**5th Annual Symposium on Coronary Stenting.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

CRITICAL CARE

January 31-February 4—**Critical Care by Design.** Society of Critical Care Medicine at Moscone Center, San Francisco. Tues-Sat. 30.5 hrs. $600. Contact: SCCM, 8101 E Kaiser Blvd, Anaheim 92808-2259. (714) 282-6000.

March 13-17—**Critical Care Medicine.** USC at Caesars Palace, Las Vegas. Mon-Fri. 33 hrs. $595-$720. Contact: USC

EMERGENCY MEDICINE

January 12-14—**Emergency Medicine.** American College of Emergency Physicians State Chapter at Ahwahnee Yosemite Lodge and Hotel, Yosemite National Park. Thurs-Sat. 25 hrs. Contact: CAL/ACEP, 505 N Sepulveda Blvd, Ste 12, Manhattan Beach 90266. (800) 735-2237.

January 16-20—**Emergency Medicine Symposium.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 24-29—**California Trauma Conference.** UCSD at Hyatt Regency, San Diego. Tues-Sun. 20 hrs. $395. Contact: UCSD.

March 6-10—**15th Annual Mammoth Mountain Emergency Medicine Ski Conference.** American College of Emergency Physicians at Mammoth Lakes. Mon-Fri. 18 hrs. $395. Contact: Daniel Abbott, MD, P.O. Box 52-B, Newport Beach 92662. (714) 650-4156.

March 13-17—**Emergency Medicine Symposium.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

May 16-17—**High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians at San Francisco. Tues-Wed. 15 hrs. $495. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 452-7475.

June 20-21—**High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians at Las Vegas, Nevada. Tues-Wed. 15 hrs. $495. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 452-7475.

EPIDEMIOLOGY/INFECTIOUS DISEASE

January 25-27—**Epidemiology and Prevention of Infectious Disease.** UCSF at Ritz-Carlton, San Francisco. Wed-Fri. 14.5 hrs. $395. Contact: UCSF.

April 2-4—**5th Annual Meeting of the Society for Healthcare: Epidemiology of America.** UCSD at Town & Country, San Diego. Sun-Tues. 17 hrs. $435. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

January 14-15—**Overview Course in Disability Evaluation.** American Academy of Disability Evaluation Physicians at Hyatt Regency Embarcadero, San Francisco. Sat-Sun. 10.5 hrs. $425. Contact: AADEP, (800) 456-6095.

January 20-22—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

January 27-30—**47th Annual Scientific Assembly—California Academy of Family Physicians.** Hyatt Regency Embarcadero. Fri-Mon. 20 hrs. Contact: Clark Franklin, CAFP, 114 Sansome St, Ste 1305, San Francisco 94104-3824. (415) 394-9121.

(Continued on Page 550)

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mupirocin

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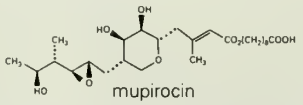
DESCRIPTION
Each gram of *Bactroban* Ointment 2% contains 20 mg mupirocin in a bland water miscible ointment base (polyethylene glycol ointment, N.F.) consisting of polyethylene glycol 400 and polyethylene glycol 3350. Mupirocin is a naturally occurring antibiotic. The chemical name is (*E*)-(2*S*,3*R*,4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxy-β-methyl-2*H*-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid. The chemical structure is:



mupirocin

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Application of ^{14}C-labeled mupirocin ointment to the lower arm of normal male subjects followed by occlusion for 24 hours showed no measurable systemic absorption (<1.1 nanogram mupirocin per milliliter of whole blood). Measurable radioactivity was present in the stratum corneum of these subjects 72 hours after application.

Microbiology: The following bacteria are susceptible to the action of mupirocin *in vitro:* the aerobic isolates of *Staphylococcus aureus* (including methicillin-resistant and β-lactamase producing strains), *Staphylococcus epidermidis, Staphylococcus saprophyticus,* and *Streptococcus pyogenes.*

Only the organisms listed in the INDICATIONS AND USAGE section have been shown to be clinically susceptible to mupirocin.

INDICATIONS AND USAGE
Bactroban (mupirocin) Ointment is indicated for the topical treatment of impetigo due to: *Staphylococcus aureus,* beta-hemolytic *Streptococcus*,* and *Streptococcus pyogenes.*

*Efficacy for this organism in this organ system was studied in fewer than ten infections.

CONTRAINDICATIONS
This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components.

WARNINGS
Bactroban Ointment is not for ophthalmic use.

PRECAUTIONS
If a reaction suggesting sensitivity or chemical irritation should occur with the use of *Bactroban* Ointment, treatment should be discontinued and appropriate alternative therapy for the infection instituted.

As with other antibacterial products prolonged use may result in overgrowth of nonsusceptible organisms, including fungi.

Bactroban is not formulated for use on mucosal surfaces. Intranasal use has been associated with isolated reports of stinging and drying.

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Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at systemic doses, i.e., orally, subcutaneously, and intramuscularly, up to 100 times the human topical dose and have revealed no evidence of impaired fertility or harm to the fetus due to mupirocin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether *Bactroban* is present in breast milk. Nursing should be temporarily discontinued while using *Bactroban.*

ADVERSE REACTIONS
The following local adverse reactions have been reported in connection with the use of *Bactroban* Ointment: burning, stinging, or pain in 1.5% of patients; itching in 1% of patients; rash, nausea, erythema, dry skin, tenderness, swelling, contact dermatitis, and increased exudate in less than 1% of patients.

DOSAGE AND ADMINISTRATION
A small amount of *Bactroban* Ointment should be applied to the affected area three times daily. The area treated may be covered with a gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.

HOW SUPPLIED
Bactroban (mupirocin) Ointment 2% is supplied in 1 gram Single Unit Packages of 50 and in 15 gram and 30 gram tubes.

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NDC 0029-1525-22 (15 gram tube)
NDC 0029-1525-25 (30 gram tube)

Store between 15° and 30°C (59° and 86°F).

DATE OF ISSUANCE MAY 1992

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Philadelphia, PA 19101

BC:L3B

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CONTINUING MEDICAL EDUCATION

(Continued from Page 549)

February 2-4—**Neurology for the Non-Neurologists.** UCSD at Doubletree Hotel, San Diego. Thurs-Sat. Contact: UCSD.

February 7-April 25—**Common Problems in Primary Care**. USC at Health Sciences Campus, Los Angeles. Tuesday Evenings. 36 hrs. $475. Contact: USC.

February 15-19—**The Practicing Physician's Approach to the Difficult Headache Patient.** Danemiller Memorial Educational Foundation at Marriott's Las Palmas Resort and Country Club, Rancho Mirage. Wed-Sun. 21.25 hrs. Contact: DHC Research & Educational Foundation, 5252 N Western Ave. Chicago, IL 60625. (312) 907-6226.

February 17-19—**Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 29-31—**Annual Review in Family Medicine**. UCSF at Hotel Nikko, San Francisco. Wed-Fri. 16 hrs. $325. Contact: UCSF.

April 10-13—**Primary Care in Paradise: Maui 1995.** Scripps Clinic and Research Foundation at Embassy Suites Resort, Kaanapali Beach, Maui, Hawaii. Mon-Thurs. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd. La Jolla 92037. (619) 554-8556.

April 27-30—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at San Diego Princess Resort. Thurs-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, P.O. Box 84296, San Diego 92138. (619) 223-2997.

GERIATRICS

January 17-20—**Intensive Course in Geriatric Medicine**. UCLA at Ritz-Carlton, Marina del Rey. Tues-Fri. 36 hrs. $675. Contact: UCLA.

March 9-10—**Practical Aspects of Caring for Alzheimer's Disease Victims**. UCSD at Pan Pacific Hotel, San Diego. Thurs-Fri. 16 hrs. $195. Contact: UCSD.

HEMATOLOGY

March 16-18—**Recent Advances in Hematopoietic Stem Cell Transplantation**. UCSD at Hyatt Regency, La Jolla. Thurs-Sat. 16 hrs. $300. Contact: UCSD.

March 30-April 1—**Current Issues in Blood Substitute Research and Development**. UCSD at Sheraton Harbor Island, San Diego. Thurs-Sat. 18 hrs. $500. Contact: UCSD.

INTERNAL MEDICINE

February 1-4—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Hyatt, San Diego. Wed-Sat. 24 hrs. $550. Contact: UCSD.

February 8-14—**Esophageal and Foregut Disorders**. USC at Hyatt Regency Hotel, Kauai, Hawaii. Wed-Tues. 30 hrs. $650. Contact: USC.

February 15-17—**Recent Advances in Neurology**. UCSF at Ritz-Carlton Hotel, San Francisco. Wed-Fri. 15.5 hrs. $365. Contact: UCSF.

February 18-23—**Topics and Advances in Internal Medicine.** UCSD at Hyatt Regency, San Diego. Sat-Thurs. 52 hrs. $595. Contact: UCSD.

February 19-24—**Emergencies in Internal Medicine: 1995**. UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $495. Contact: UCD.

February 25—**Sjogren's Syndrome: A Symposium for Patients and Professionals.** USC at Louis B. Mayer Teaching Center, Los Angeles. Sat. 4.5 hrs. $85. Contact: USC.

March 17-23—**Internal Medicine 1995: A Comprehensive Review.** Continuing Medical Education Associates at Hotel del Coronado. Fri-Thurs. 54 hrs. $695. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 25-April 1—**Diagnostic and Therapeutic Skills in Internal Medicine.** USC at Hapuna Prince Hotel, Kamuela, Hawaii. Sat-Sat. 29 hrs. $595. Contact: USC.

(Continued on Page 551)

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Please see complete prescribing information on adjacent page.

CONTINUING MEDICAL EDUCATION

(Continued from Page 550)

April 22-23—**Minimal Intervention in Vascular Disease.** Scripps Memorial Hospital and Scripps Clinic and Research Foundation at Hyatt Regency, San Diego. Sat-Sun. Contact: Laurel Steigerwald, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OB/GYN

February 9-12—**50th Annual Postgraduate OB/GYN Assembly.** Obstetrical and Gynecological Assembly of Southern California at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OGASC, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

February 18-24—**Perinatal Medicine.** USC at Westin Maui Hotel, Hawaii. Sat-Fri. 30 hrs. $595. Contact: USC.

ONCOLOGY

February 20-23—**Clinical Hematology and Oncology: 1995.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 28 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 10-14—**20th Annual Conference: Diagnostic Approaches to Lymphoproliferative Disorders.** Scripps Clinic and Research Foundation at Ritz-Carlton, Maui, Hawaii. Mon-Fri. 26 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OPHTHALMOLOGY

January 14—**Primary Care Ophthalmology.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

February 17-18—**Comprehensive Cosmetic Blepharoplasty: Options and Finesse.** UCLA Jules Stein Institute. Fri-Sat. 16 hrs. $250. Contact: Angela O'Mara-Barnes, Meeting Coordinator, 359 San Miguel Dr, Ste 303, Newport Beach 92660. (714) 760-1522.

June 2—**Annual UCD Ophthalmology Symposium.** UCD at Vizcaya Pavilion, Sacramento. Fri. 6 hrs. $95. Contact: UCD.

ORTHOPEDICS

May 18-21—**10th Annual Symposium of the Spine Study Group.** Spine Study Group at Westin Mission Hills, Rancho Mirage. Thurs-Sun. Contact: Pat Curl, Meeting Coordinator, 4805 Mercury St, Ste E, San Diego 92111. (619) 279-9955.

OTOLARYNGOLOGY

January 8-13, February 5-10—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 55 hrs. $1,100-1,300. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

June 25-30—**Sacramento International Skull Base Surgery Symposium: A Multidisciplinary Approach.** UCD at Hyatt Regency, Sacramento. Sun-Fri. $450. Contact: UCD.

PATHOLOGY

April 1—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundtion. Sat. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 25-27—**Current Issues in Anatomic Pathology: 1995.** UCSF at Mark Hopkins Intercontinental Hotel, San Francisco. Thurs-Sat. 19.5 hrs. $195-$495. Contact: UCSF.

PEDIATRICS

January 21-28—**Pediatric Emergencies.** UCSD at Kona, Hawaii. 21 hrs. $460. Contact: UCSD.

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★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

HIV 7TH NATIONAL AIDS UPDATE CONFERENCE

"Health Care Reform: HIV Today and Tomorrow"

January 31 - February 3, 1995
San Francisco Moscone Convention Center

***Conference Sponsors** (partial list)*

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California Department of Health Services
California Medical Association
California Nurses Association
International Society for AIDS Education
Kaiser Family Foundation
Kaiser Permanente Northern California
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National Association of Counties
National Association of People with AIDS
National Association of Social Workers
National Catholic AIDS Network
National Coalition of Hispanic Health and Human Services Organizations (COSSMHO)
National Hospice Organization
National Minority AIDS Council
San Francisco Department of Public Health
San Mateo County AIDS Program
United States Conference of Mayors
University of California EPI Center at San Francisco General Hospital
University of California San Francisco/ AIDS Health Project
Visiting Nurses and Hospice of San Francisco

The primary goal of this Conference is to provide opportunities for discussion among health care service providers, policy makers, funders, educators and program administrators, and persons living with HIV to find the best means to meet the special challenges which the HIV/AIDS epidemic poses.

The Conference is especially relevant for:

- physicians
- policy-makers
- health care providers
- people with HIV/AIDS
- nurses
- pharmacists
- public health agencies
- mental health practitioners
- dentists
- social workers
- program administrators
- government and community leaders
- community-based and HIV/AIDS service organizations, administrators and caregivers
- hospital service and planning managers

Plenary Sessions, nearly 100 Workshops, and nine Intensive Workshops are presented for various levels of attendee knowledge and expertise and bring attention to HIV/AIDS issues in five Conference tracks:

• Policy and Administration • Prevention and Education • Care and Services • Treatment • Cultural Issues

Special events include: Roundtable Talks, Poster Sessions, Film and Theater Festivals, an AIDS in the Arts Display, Resource Center Exhibits, an HIV/AIDS Book Fair, and a display of The NAMES Project AIDS Memorial Quilt.

***Confirmed Speakers To Date** (partial list)*

Inge Corless, PhD, RN, FAAN, Massachusetts General Hospital, Institute of Health Professions, Boston, MA
Elaine Daniels, MD, PhD,Chief, Health Professions, HIV Education Branch, U.S. Public Health Service, Rockville, MD
Donald P. Francis, MD, DSc, Genentech, South San Francisco, CA
Loretta Sweet Gemmott, RN, PhD, FAAN, Assoc. Professor & Dir. of Center for AIDS Research, School of Nursing, Columbia University, NYC
Philip R. Lee, MD, Assistant Secretary for Health, Dept. of Health and Human Services, Washington, DC
Jeff Levi, AIDS Action Council, Washington, DC
Mervyn F. Silverman, MD, MPH, President, AMFAR, Los Angeles, CA
Richard L. Sowell, PhD, RN, FAAN, AID Atlanta, Inc., Atlanta, GA
Paul Volberding, MD, Professor of Medicine, University of California San Francisco. Director, AIDS Program, San Francisco General Hospital, CA

Applications have been submitted for up to 20.5 hours of CME and CEU credit for physicians, nurses and social workers

For general information, to register or exhibit, contact:
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PROGRAM PROFILE

Center for Arthritis and Joint Implant Surgery

The Center for Arthritis and Joint Implant Surgery at USC University Hospital is dedicated to bringing patients the combined proficiency of an experienced team, plus the distinct advantage of a university-based research program.

A Team Approach

Difficult and complex surgical procedures for the treatment of arthritis and joint replacements are offered at the Center. The staff has been working together as a team for 10 years and participates in:

- Surgical evaluation and planning
- Pre-operative patient education and medical evaluations
- Post-operative pain management and rehabilitation
- Extended care rehabilitation/management
- Close contact with referring physicians
- Grand rounds for physicians

Research Advantage

The Center conducts continuing research in the field of arthritis and joint implant surgery, specifically:

- Research into coatings along the surfaces of implants that increase the ability of the implant to stay bonded with bone.
- Research into articular surfaces that decrease wear and increase longevity of implants.
- Development of medicines that accelerate the healing process of bone around implants and secure prosthesis to bone.
- Ongoing design and development of new implant systems incorporating advances in metallic alloys and plastic technology.
- Development of surgical techniques that minimize muscular and ligament damage.

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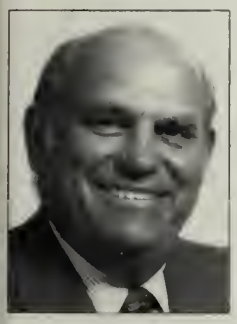

***Lawrence D. Dorr, M.D.**, director of the Center for Arthritis and Joint Implant Surgery at USC University Hospital, and professor of Orthopaedic Surgery at the University of Southern California School of Medicine, is a leader in joint replacement research, authoring more than 100 scientific articles. He has extensive surgical experience in joint replacement, which includes 2,500 hip and knee replacements in the past decade alone. He was named in the text of "Best Doctors in America" for 1992-1993.*

Dr. Dorr was the designer for the APR hip system, a pioneer in bone ingrowth fixation. He also designed the Apollo Hip and Knee Systems, which are modern cemented implants designed for economical longevity.

***Edward J. McPherson, M.D.**, assistant professor of Orthopaedic Surgery at the University of Southern California School of Medicine, is a member of the Center for Arthritis and Joint Implant Surgery at USC University Hospital. Dr. McPherson will head the revision service at the Center.*

Dr. McPherson's research interests include hip pain in athletes, the study of surface coatings to enhance bone ingrowth fixation in hip and knee replacements, and the study of articular surface coatings to reduce friction and wear. Additionally, Dr. McPherson has specialized interest and training in revision arthroplasty of the hip and knee, as well as experience with reconstruction and replacement of the shoulder and elbow.

***Desmond M. Dall, M.D., F.R.C.S.**, professor of Clinical Orthopaedics at the University of Southern California School of Medicine, is a member of the Center for Arthritis and Joint Implant Surgery at USC University Hospital.*

Dr. Dall has several major areas of research interest, including reconstructive surgery of the hip and knee, comparative functional evaluation of different antero-lateral approaches to the hip joint in total hip replacements, and the effect of muscular activity on the hip and endoprosthesis fixation. He also is investigating new fixation techniques in high tibial osteotomy and development of new techniques of internal fixation of long bones.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 551)

January 23-27—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital San Diego at Town and Country Hotel, San Diego. Mon-Fri. $395. Contact: Children's Hospital, MC 5016, 3020 Children's Way, San Diego 92123. (619) 495-4940.

February 4—**Update in Behavioral and Developmental Pediatrics.** UCSF at Millberry Union Conference Center, San Francisco. Sat. 6.5 hrs. $110. Contact: UCSF.

February 20-22—**Pediatrics Update 1995.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 3-5—**Current Concepts in Pediatric Medicine.** Children's Hospital San Diego at Catamaran Resort Hotel, San Diego. Fri-Sun. $365. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

March 31-April 1—**Pediatric Dermatology for the Practitioner.** Children's Hospital and Health Center and UCSD at Hyatt Regency, La Jolla. Fri-Sat. 12.75 hrs. $245. Contact: Children's Hospital, 3020 Children's Way-5021, San Diego 92123. (619) 576-4072.

May 4-6—**28th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

June 23-25—**Current Concepts in Pediatric Respiratory Diseases.** Children's Hospital San Diego and UCSD at San Diego Princess Resort. Fri-Sat. 16 hrs. Contact: Children's Hospital, 3020 Children's Way-5021, San Diego 92123. (619) 576-4072.

PSYCHIATRY

January 22-27—**21st Annual Midwinter Program for Psychiatrists.** UCD at Incline Village, Nevada. Sun-Fri. 25 hrs. Contact: UCD.

February 23-26—**Breakthroughs in Psychiatry and the Law: Dangerousness and Its Discontents.** UCSD at La Jolla Marriott. Thurs-Sun. 15.5 hrs. $310. Contact: UCSD.

March 31-April 2—**West Coast Psychiatry Board Review: Preparation for Part II.** UCSD at La Jolla Marriott. Fri-Sun. 16 hrs. $525. Contact: UCSD.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs. (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

PULMONARY MEDICINE

January 26-28—**Pulmonary Medicine and Surgery: New Approaches to Diagnosis and Treatment.** UCSD at Hotel del Coronado. Thurs-Sat. 18 hrs. $500. Contact: UCSD

January 28—**Rhinitis—Sinusitis and Atopic Dermatitis: Evaluation, Treatment, Mechanisms, and Relevance to Asthma.** Huntington Memorial Hospital at Braun Auditorium, Pasadena. Sat. Vivian Mishalany, 39 Congress St, Ste 301, Pasadena 91105. (818) 397-3383.

February 3-5—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Sheraton Desert Inn, Las Vegas, Nevada. Fri-Sun. 12 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528.

RADIOLOGY

March 5-9—**Neuro and Musculoskeletal MR.** UCSD at Hotel del Coronado, San Diego. Sun-Thurs. 30 hrs. $600. Contact: Dawne Ryals, Ryals & Associates, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 5-10—**General Radiology Review.** UCLA at Guest Quarters Suite Hotel, Santa Monica. 40 hrs. $420. Contact: UCLA.

March 5-10—**Magnetic Resonance Imaging of the Brain, Spine, and Musculoskeletal System.** UCSD at Hotel del Coronado. Sun-Fri. 30 hrs. $625. Contact: UCSD.

March 10-12—**Musculoskeletal Imaging.** UCSD at Hotel del Coronado. Fri-Sun. Contact: UCSD.

March 13-15—**15th Annual Current Approaches to Radiation Oncology, Biology, and Physics.** UCSF at Hotel Nikko, San Francisco. Mon-Wed. 18 hrs. $350. Contact: UCSF.

April 16-21—**15th Annual Residents' Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $600. Contact: Dawne Ryals, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 21—**Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. 8 hrs. $135. Contact: Dawne Ryals, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 21-23—**Mammography Update and Review.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 16 hrs. $350. Contact: Dawne Ryals, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

SLEEP MEDICINE

January 28—**Sleep Medicine: Practices for the 21st Century.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

SURGERY

January 13-14—**What's New in General Surgery: 17th Annual Postgraduate Course.** UCD at Hyatt Hotel, Sacramento. 15 hrs. Contact: UCD.

January 13-15—**Annual Meeting of the California Association of Neurological Surgeons**: Health Care Reform. California Association of Neurological Surgeons at Four Seasons Hotel, Newport Beach. Fri-Sun. 7 hrs. Laurie Alexander. (916) 971-3524.

February 3-4—**Colon and Rectal Surgery.** USC at Ritz-Carlton Huntington Hotel, Pasadena. Fri-Sat. Contact: USC.

February 6-10—**18th Annual San Diego Postgraduate Assembly in Surgery.** UCSD at Hyatt Islandia, San Diego. Mon-Fri. 26 hrs. $475. Contact: UCSD.

February 11-12—**Endoscopic Plastic Surgery and Beyond.** UCSD at BSB and Thornton Hospital, La Jolla. Sat-Sun. 13 hrs. $1250. Contact: UCSD.

March 24-25—**7th Annual Symposium on Aesthetic Surgery of the Face.** UCSF at San Francisco. Fri-Sat. Contact: UCSF.

April 20-22—**Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton Hotel, Nob Hill, San Francisco. Thurs-Sat. Contact: UCSF.

April 29-30—**Endoscopic Plastic Surgery and Beyond.** UCSD at UCSD BSB and Thornton Hospital, La Jolla. Sat-Sun. 13 hrs. $1250. Contact: UCSD.

GENERAL/MULTIDISCIPLINARY

February 13-16—**Topics in Clinical Medicine: Evidence Based Care Conference.** Group Health Cooperative of Puget Sound at Royal Waikoloan, Kona, Hawaii. Mon-Thurs. 19 hrs. $450. Contact: Group Health Cooperative, CEB-1, 201 16th Ave E, Seattle, WA 98112. (206) 326-3441.

(Continued on Page 558)

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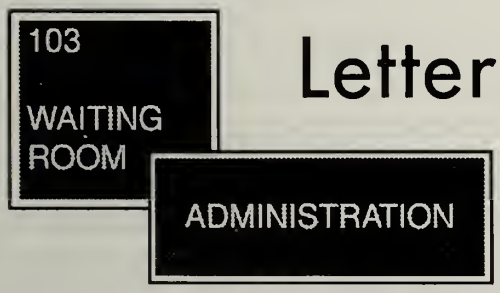

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February 13-17—**Physician Heal Thyself.** UCSD at Sheraton Harbor Island, San Diego. Mon-Fri. Contact: UCSD.

February 16-19—**2nd International Congress on Vitamins and Biofactors in Life Science.** Thurs-Sun. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 18-21—**Molecular Approaches to Laboratory Diagnosis.** UCSF at Ritz-Carlton, San Francisco. Sat-Tues. Contact: UCSF.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

January 28-February 2—**24th Annual Mid-Winter Conference of Colorado Ophthalmological Society.** Sheraton Steamboat, Steamboat Springs. Sun-Thurs. Contact: David R Scott, (800) 394-4968.

February 20-24—**19th Midwinter Symposium on Practice Surgical Challenges in Otolaryngology.** University of Illinois College of Medicine at Snowmass. Mon-Fri. Contact: Jane Whitener, (312) 996-5751.

February 26-March 3—**Ninth Annual Cardiology for the Clinician Conference: Practical Guidelines for Merging Advances in Cardiology and Bedside Medicine.** University of Illinois College of Medicine at Snowmass. Mon-Fri. Contact: Sue Talbert, (312) 996-4631

March 5-10—**15th Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Medical Center. (402) 559-4152 or (800) 642-1095; FAX (402) 559-5915.

March 12-15—**5th International Conference on Pulmonary Rehabilitation and Home Ventilation.** National Jewish Center for Immunology and Respiratory Medicine and American Association for Respiratory Care at Hyatt Regency, Denver. Sun-Wed. Contact: Adele Gelfand, (303) 398-1359 or 270-2171.

July 28-August 1—**80th Annual Summer Conference.** Colorado Ophthalmological Society at Sheraton Steamboat Resort, Steamboat Springs. Fri-Tues. Contact: David R. Scott, (800) 394-4968; FAX (303) 438-9602.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 270-6761.

IDAHO

February 17-19—**Ada County Medical Society—36th Annual Medical Winter Clinics—From Trauma to Rehab.** Shore Lodge Inn, McCall. Fri-Sun. 9 hrs. $125, members: $175, nonmembers. Contact: Ada County Medical Society, Box 2668, Boise 83701; Judy Barningham, (208) 336-2930 or Marie Chester, (208) 386-2135.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

April 22—**New Mexico Society of Anesthesiologists—Annual Meeting** Hilton Hotel of Santa Fe. Sat. Contact: Lynette Hanks, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237 or (800) 748-1596.

July 3-7—**Santa Fe Breast Imaging.** Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925.

July 7-9—**Health Care Revolution: Where Do We Go From Here?** Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 3-6—**Sport Medicine and Imaging.** Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925 (404) 641-9773.

August 7-11- **Imaging 1995.** Eldorado Hotel, Santa Fe. Contact: Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

January 17-22—**Advances in Craniofacial/Oculoplastic and Facial Aesthetic Surgery.** University of Utah School of Medicine at the Cliff Lodge at Snowbird. Tues-Sun. 24 hrs. $525. Contact: UUSM.

January 23-27—**Workshops in Advances MR Imaging, Head and Neck Imaging, and Neuroradiology.** University of Utah School of Medicine. Mon-Fri. Contact: UUSM.

February 6-10—**Surgical Pathology.** University of Utah School of Medicine at the Yarrow Hotel, Park City. Mon-Fri. 20 hrs. $550. Contact: UUSM.

February 20-24—**Workshops in Advanced MR Imaging, Head and Neck Imaging, and Neuroradiology.** University of Utah School of Medicine. Mon-Fri. Contact: UUSM.

(Continued on Page 560)

Remember, It's Time to Send in Your CME Forms.

The California Medical Association (CMA) is encouraging its members as well as nonmember physicians to respond to the CME Certification Program's mailing of its annual continuing medical education (CME) reporting form, scheduled for this month.

In its 25th year, the Certification Program continues to provide physicians with a system of documenting and verifying participation in Category 1 approved, post-graduate education and other acceptable Category 1 CME.

Physicians using this service compile a yearly summary of their CME activities to report to CMA. Courses and hours are verified for compliance to CME standards as set by CMA and the Medical Board of California (MBC). Acknowledgement letters are mailed within four to six weeks. MBC endorses participation in the CME Certification Program for meeting state relicensing requirements. Annual reporting satisfies eligibility for CMA's Certificate in Continuing Medical Education and the American Medical Association's Physician Recognition Award. Physicians also may obtain documentation or instruct institutions to request CME records directly from CMA for hospital, HMO, or PPO credentialing, and to renew membership in medical specialty organizations.

CMA members are entitled to free documentation of CME activity; nonmembers are charged a fee of $39. For medical staffs who wish to request physician CME records, fax or write a letter which states the year(s) for which documentation is needed. Include the physician's California license number and a signed release form. Also specify whether a report of hours and/or copies of reporting forms are needed. A processing fee will be assessed.

As a reminder, CMA cautions physicians to select CME activities carefully. To avoid attending "bogus" CME courses, physicians should look for the CME logo and/or language identifying the provider as CMA or ACCME accredited. Only CME accredited programs are eligible for Category 1 credit hours. Be wary of statements indicating that CME credit "is being applied for" or "will be available" or that an organization is in the process of applying for accreditation. These statements are worded so that physicians are misled into thinking that Category 1 credit will be awarded.

For more information on the CME Certification Program and licensing, waiver requirements, available CME courses and accredited providers, contact **Karen Williams, CME Certification, P.O. Box 7690, San Francisco 94120. ph (415) 882-5183; fx (415) 882-3332.**

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CONTINUING MEDICAL EDUCATION

(Continued from Page 558)

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 26—**Cancer Care Symposium**. Seattle. Thurs. Contact: Providence, (206) 320-2552.

March 2—**Emergency Response in the Workplace: An Occupational Health Nursing Update.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

April 13—**Advances in Occupational and Environmental Medicine**. Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762. ◆

In Memoriam

California Medical Association

Brechner, Verne L., Santa Monica. Died Sep 11, 1994, aged 70. Graduate of Washington University School of Medicine, St Louis, Missouri, 1948. Licensed in California in 1953. Dr Brechner was a member of the Los Angeles County Medical Association.

Falkner, Robert E., Stockton. Died Oct 9, 1994, aged 54. Graduate of Northwestern University Medical School, Chicago, Illinois, 1966. Licensed in California in 1967. Dr Falkner was a member of the San Joaquin County Medical Society.

Fisher, Allan J, Palm Springs. Died Mar 27, 1994, aged 66. Graduate of University of Rochester School of Medicine, Rochester, New York, 1952. Licensed in California in 1954. Dr Fisher was a member of the Riverside County Medical Association.

Friedrich, Erwin Hans, Escondido. Died Oct 1994, aged 86. Graduate of Julius Maximilians University, Germany, 1944. Licensed in California in 1965. Dr Friedrich was a member of the San Diego County Medical Society.

Happee, Dirk Jr, Freedom. Died Sep 30, 1994, aged 69. Graduate of University of Leiden, Holland, 1959. Licensed in California in 1963. Dr Happee was a member of the Santa Cruz County Medical Society.

Heckman, John R., Marysville. Died Sep 24, 1994, aged 72. Graduate of University of Vermont College of Medicine, Burlington, 1951. Licensed in California in 1954. Dr Heckman was a member of the Yuba-Sutter-Colusa County Medical Society.

Iverson, Herman A., Trinidad. Died Oct 6, 1994, aged 78. Graduate of Johns Hopkins University School of Medicine, Baltimore, Maryland, 1941. Licensed in California in 1945. Dr Iverson was a member of the Humboldt-Del Norte Medical Society.

Jantzen, Roland R., Redding. Died Oct 14, 1994, aged 84. Graduate of University of California, San Francisco, School of Medicine, 1936. Licensed in California in 1936. Dr Jantzen was a member of the Shasta-Trinity County Medical Society.

Manuele, Angelo, Visalia. Died Oct 3, 1994, aged 66. Graduate of California College of Medicine, Irvine, 1962. Licensed in California in 1975. Dr Manuele was a member of the Tulare County Medical Society.

Michaels, Peter A., Sacramento. Died Aug 2, 1994, aged 62. Graduate of Loyola University of Chicago Stritch School of Medicine, Chicago, Illinois, 1958. Licensed in California in 1964. Dr Michaels was a member of the Sacramento-El Dorado Medical Society.

Michel, Francis W., Mountain View. Died Sep 25, 1994, aged 65. Graduate of Washington University School of Medicine, St Louis, Missouri, 1955. Licensed in California in 1956. Dr Michel was a member of the Santa Clara County Medical Association.

Mudry, Joseph, Palm Desert. Died Aug 3, 1994, aged 81. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1939. Licensed in California in 1939. Dr Mudry was a member of the Riverside County Medical Association.

Neufeld, Ronald Samuel, San Diego. Died Sep 17, 1994, aged 44. Graduate of Case Western Reserve University School of Medicine, Cleveland, Ohio, 1978. Licensed in California in 1980. Dr Neufeld was a member of the San Diego County Medical Society.

Pambakian, Robert, Delmar. Died Sep 30, 1994, aged 46. Graduate of American University of Beirut, 1973. Licensed in California in 1978. Dr Pambakian was a member of the San Diego County Medical Society.

Pappenfort, Roberts B., San Diego. Died Oct 7, 1994, aged 76. Graduate of Washington University School of Medicine, St Louis, Missouri, 1943. Licensed in California in 1946. Dr Pappenfort was a member of the San Diego County Medical Society.

Denver Medical Society

Bricker, John William. Died Oct 4, 1994, aged 83. Graduate of University of Michigan Medical School, Ann Arbor, 1940. Licensed in Colorado in 1946.

New Mexico Medical Society

Bromme, Dorothy A., Santa Fe. Died Oct 5, 1994, aged 68. Graduate of University of Colorado School of Medicine, Denver, 1955. Licensed in New Mexico in 1959. Dr Bromme was a member of the Santa Fe County Medical Society.

Spensley, Robert D., Albuquerque. Died Oct 21, 1994, aged 75. Graduate of New Mexico University Medical School, Albuquerque, 1949. Licensed in New Mexico in 1952. Dr Spensley was a member of the Greater Albuquerque Medical Association.

Wyoming Medical Society

Werner, Michael H., Rock Springs. Died Sep 21, 1994, aged 50. Graduate of Wayne State University School of Medicine, Detroit, Michigan, 1970. Licensed in Wyoming in 1978. Dr Werner was a member of the Sweetwater County Medical Society.

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2. Location of the headquarters or general business office of the publisher: 221 Main Street, 3rd Floor, San Francisco, California 94105.

3. Publisher: California Medical Association, 221 Main Street, 2nd Floor, San Francisco; Editor, Linda Hawes Clever, MD, 221 Main Street, 3rd Floor, San Francisco, California 94105; Managing Editor, Diana McAninch, 221 Main Street, 3rd Floor, San Francisco, California 94105.

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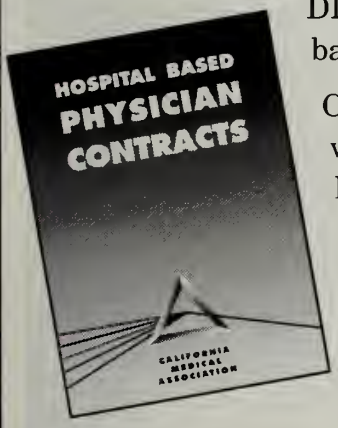

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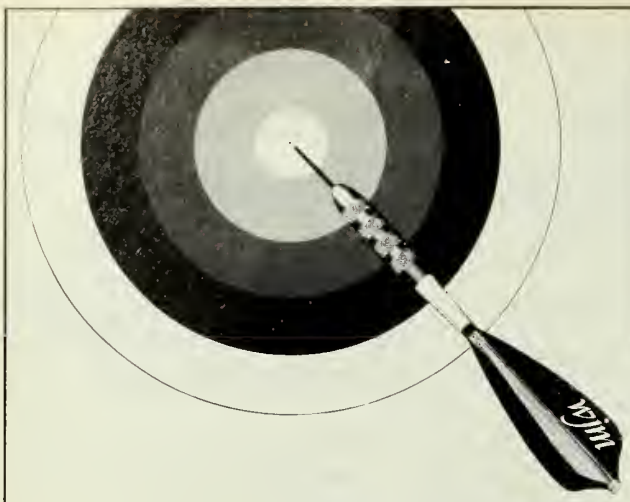

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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

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Articles

Firearm Violence in California

Information and Ideas for Creating Change

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This paper was chosen as the winner of THE WESTERN JOURNAL OF MEDICINE'*s 1994 Medical Student Writing Competition. The contest was open to all students attending medical schools in the West and is repeated annually.*

LINDA HAWES CLEVER, MD
Editor

Homicides have been on the rise in California in recent years, almost entirely as a result of increased firearm activity, resulting in one of the highest homicide rates in the country. With increasing morbidity and mortality from guns, health care professionals have called the situation an epidemic. In the past decade, attention from the health care profession has resulted in a new focus on the public health issues surrounding firearms. There is considerable confusion among policy makers regarding what should be done to stem firearm violence. I discuss morbidity and mortality trends, academic research, and legal issues surrounding firearm violence, affording insight into the seriousness and complexity of this rapidly growing problem and providing policy ideas for addressing the role of firearms. Such policy ideas include removal of the California Legislature's preemptive authority on firearms licensing and registration; the formation of an information and advisory body within the California Department of Health; increased liability for manufacturers, distributors, dealers, and owners; and a statewide registration system.

(Kahn JB: Firearm violence in California—Information and ideas for creating change. West J Med 1994; 161:565-571)

Between 1985 and 1991, mortality from firearms in California rose from 3,828 to 5,048 deaths (Tables 1 and 2).[1] By comparison, motor vehicle accidents in that year accounted for 4,900 deaths.[2] More deaths from firearm trauma than by motor vehicle accidents was a first for California in 1991. Motor vehicle accidents outnumbered firearms as a leading cause of death in 1985; the change in rank between deaths caused by firearms and motor vehicle accidents by 1991 came mostly as a result of an increase in deaths from firearms, not from a decrease in fatalities in motor vehicle accidents.[1-4]

In 1987 firearm deaths and injuries in California were described as an "epidemic of modern times."[5] Considering the recent increases in firearm mortality, this epidemic has continued and is becoming more severe. Health care professionals increasingly view firearm violence as an important public health issue.[5-9] In this article I review statistics, scientific studies, and legal issues surrounding firearm violence in California.*

*See also the editorial by A. L. Kellermann, MD, MPH, "Do Guns Matter?" on pages 614-615 of this issue.

Firearm Mortality and Morbidity

During 1987, California had the highest rates in the United States for both total and firearm-related homicides among 15- to 24-year-old white men and the second highest such rates among African-American men aged 15 to 25 years.[12] This ranking is especially important because both nationally and in the state of California, members of this age group are the victims of more firearm fatalities than any other and because among young African Americans, firearm violence is the leading cause of death.[10-12]

In 1991, California had one of the highest overall rates of homicide in the United States at 12.7 deaths per 100,000 residents.[13] Nearly 70% of California's homicides were from firearms (Table 1). Between 1985 and 1991, an increase of 32% in firearm-related mortality in the state was due entirely to an increase in homicides involving firearms,[1] but other causes of death from firearms actually decreased or remained constant (Table 2).

Since 1950, murders with firearms have accounted for nearly the entire increase in homicides throughout the United States.[14] In addition, between 1985 and 1991, the

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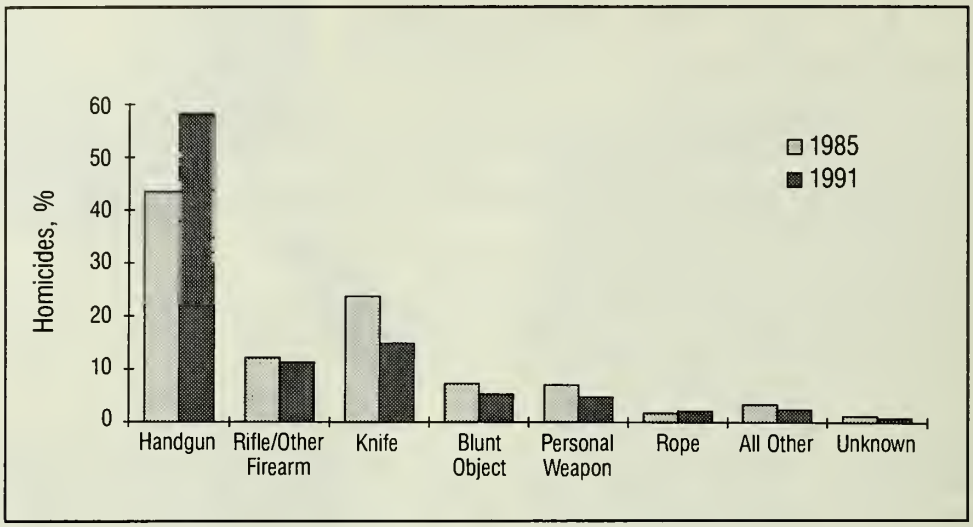

Figure 1.—Percentages of homicides in California in 1985 and 1991 are shown by type of weapon.

use of firearms was the dominant factor in the rising rate of homicides (Table 3).[15] In particular, the increase in firearm-related homicides was almost entirely as a result of the increase in homicides with handguns. As shown in Figure 1, handguns are by far the predominant weapon used in homicides in California.[11]

Morbidity from firearms has been difficult to assess, given poor classification of nonfatal firearm injuries and the incompatibility between injury classification systems.[6] Recent estimates of the total number of firearm-related injuries from causes other than suicide range from five to seven times the number of deaths, with firearm injuries requiring admittance to hospitals numbering approximately twice the number of deaths.[6,16,17] For suicide, the rates of completion with a firearm approximate 98%.[16]

The use of firearms during violent acts, such as robbery and aggravated assault, has been increasing rapidly (Table 4).[18] As the incidence of crimes involving firearms increases, the potential for persons to be killed rises as well. In a physical attack, the chance of death is approximately three to five times greater when the perpetrator uses a gun rather than a knife, and the chance is 12 times greater than with all nonfirearm weapons.[19-21]

The situation is likely to become worse because violent crimes likely to involve firearms are being committed with increasing frequency by youths. According to 1991 data of felony arrests, 60.4% of all persons arrested for homicide and 62.4% of those arrested for robbery were younger than 25 years.[18] Rates of arrest and the percentage of increase in rates of arrest between 1985 and 1991 for homicides, robberies, and forcible rapes were substantially greater among juveniles aged 10 to 17 years than among adults aged 18 and older (Tables 5 and 6).

Growth of Gun Supply

As the rates of deaths and violent acts involving firearms has grown, so, too, has the supply of guns. In the United States, nearly 50% of all American households contain at least one of the estimated 200 million firearms in circulation.[6,22] Although official estimates of the number of guns in California are not available, the state has experienced a tremendous growth in its firearm supply, according to records from its 11,462 federally licensed gun dealers.[23]

In 1992, a total of 367,375 handguns and 177,486 long guns such as rifles and shotguns were legally purchased in California.[23,24] From 1986 to 1992, sales of handguns alone increased from 254,479 to 367,375 guns a year.[23] In this seven-year period, 2,100,190 handguns were purchased legally, an average of 300,027 handguns a year. This figure represents approximately 800 hand-

TABLE 1.—*California Deaths From Firearms and Motor Vehicle Accidents (MVAs) With Percentage Contribution of Change Between 1985 and 1991**

Cause of Death	1985	1991	Change No.	Change (%)	Contribution to Total Change, %
Firearms	3,828	5,048	+1,220	(+32)	75
MVAs†	5,296	4,900	−396	(−7.5)	25
Total change			1,616		100

*From California Department of Health Services.[13]

†Defined as those involving California residents. In 1991, there were even fewer MVA deaths occurring within the boundaries of California. From California Department of Finance.[4]

TABLE 2.—*California Firearm Deaths by Specific Use, 1985 to 1991**

Cause of Death	1985 No.	1985 Rate†	1991 No.	1991 Rate†	Percent Change, No.	Percent Change, Rate†
Homicides	1,585	6.0	2,898	9.5	+82.7	+58.3
Suicides	2,013	8.0	1,950	6.4	−3.1	−20.0
Accident	151	1.0	126	0.4	−16.6	−60
Legal intervention	53	0.2	53	0.17	0.0	−15
Intent unknown	26	0.1	23	0.08	−11.5	−20
Total	3,828	14.5	5,048	16.6	+31.9	+14.5
Population	26,365,000		30,380,000			

*From California Department of Health Services.[1]

†Rates are per 100,000 of all California citizens.

TABLE 3.—*Total Firearm-Related Homicides in California, 1985 to 1991**

Type of Homicide	1985	1991	Change No.	Change %
Total	2,818	4,071	+1,253	+44.5
Firearm-related	1,585	2,896	+1,311	+82.7

*From California Department of Health Services.[15]

guns sold each day through the legal, recorded transactions of federally licensed firearms dealers.

Illegal Gun Ownership

No official data are available for guns that are obtained illegally, but recent reports estimate that 70% to 80% of guns used by criminals are stolen or purchased illegally.[25,26] As the supply of lawfully purchased firearms in California homes increases, criminals can more easily obtain firearms to be used unlawfully. In a 1989 survey of 605 firearm owners throughout the United States, only 45% reported keeping their firearms locked up when not in use.[27] In addition, 56% of those surveyed reported owning three or more firearms.

Pros and Cons of Gun Ownership

Statistical data are alarming, but such statistics do not make clear whether guns themselves affect gun violence. Understanding this relationship helps educate the public and creates a direction for policy on firearms.

Benefits of Guns

Despite their use in violent crime and death, guns have benefits for society. The most evident benefit is recreation for millions of sharpshooters and hunters. Protective claims have been related anecdotally, but no case-controlled or statistically generalizable research has ever shown that the presence of a firearm as protection during an attack is associated with a decreased risk of morbidity and mortality.[28] The existing evidence is from surveys of personal accounts of self-protection,[29] and the validity of such accounts has not been substantiated.

Many gun advocates insist that if every citizen possessed a firearm, criminals would be deterred from committing crimes. With at least half of all American households owning firearms,[6,22] however, crime rates continue to rise. Perhaps more important, gun advocates have been unable to respond adequately to the increasing evidence that in California, as in the rest of the nation, most firearm-related violence is being committed by relatives and friends of victims and in the course of arguments.[12,13]

TABLE 4.—*Change in Firearm and Knife Use in Reported Violent Acts in California, 1985 to 1991**

Violent Act	1985	1991	% Change
Robbery			
All weapons†	86,464	125,105	+45
Firearms	29,829	44,933	+51
Knives	12,293	15,128	+23
Assault			
All weapons	101,379	188,993	+86
Firearms	19,434	40,063	+106
Knives	19,348	24,878	+28

*From California Department of Justice.[18]
†Refers to violent acts committed with firearms, knives, blunt object, rope, and personal weapons such as hands and feet.

TABLE 5.—*California Juvenile Arrests for Selected Felony Crimes, 1985 to 1991**

Felony Crime	1985 No.	1985 Rate†	1991 No.	1991 Rate†	Percent Change, No.	Percent Change, Rate†
Homicides	236	8.3	696	20.9	+195	+152
Robbery	5,180	181.6	7,960	239.4	+53.7	+31.8
Forcible rape	481	16.8	665	20.0	+38.2	+19.0
Felony assault	6,366	223.1	11,695	351.7	+83.7	+57.6
Total	12,263	429.8	21,016	632.1	+71.4	+47.1
Population	2,835,000		3,324,900			

*From California Department of Justice.[18]
†Rates are per 100,000 California youths aged 10-17 years.

Problems With Guns

In California during 1991, most homicides (64.9%), occurred between relatives, friends, or acquaintances.[12] Of all female victims, 22.4% were murdered by a spouse. The relationship between victim and offender was unknown for 1,318 cases. According to the California Department of Justice, although including these unknowns would increase the statistics for stranger homicides relative to other relationships, friends and acquaintances would remain the most frequent relationship between victim and murderer. Furthermore, of those cases of homicide where the precipitating event was known, 43% were caused by arguments, with only 16.4% occurring in the course of a rape, robbery, or burglary and an additional 30.4% occurring as a result of drug- or gang-related activity. In addition, using estimates from several studies, a "reasonably conservative estimate" of the proportion of homicide offenders with previous felony convictions is 25%, indicating that perhaps 75% of all homicides are committed by persons without previous felony records.[19]

Because 71.1% of all homicides are committed with a gun,[15] usually a handgun,[12] the mere presence of firearms in society may play an important role in the rising rates of mortality. Kellermann and co-workers reported in a case-

TABLE 6.—*California Adult Arrests for Selected Felony Crimes, 1985 to 1991**

Felony Crime	1985 No.	1985 Rate†	1991 No.	1991 Rate†	Percent Change, No.	Percent Change, Rate†
Homicides	2,884	15.0	3,024	13.5	+4.8	−10.0
Robbery	19,074	99.3	23,386	104.6	+22.6	+5.3
Forcible rape	3,733	19.4	3,752	16.8	+0.5	−13.4
Felony assault	38,695	202	92,792	415.1	+140	+105.5
Total	64,386	335	122,954	550	+90.1	+64.2
Population	19,200,300		22,354,600			

*From California Department of Justice.[18]
†Rates are per 100,000 California adults aged 18 years and older.

controlled, population-based study of three counties in Tennessee, Washington, and Ohio that the presence of a gun in the household triples the risk of a household member being murdered with a firearm.[30] This threefold increase in risk exists even after adjusting for location and for household members with previous arrests, illicit drug use, and histories of nonfatal domestic fighting. This study also found that approximately 51% of the homicides followed altercations and that at least 77% of homicides occurred between relatives and acquaintances. Earlier research also supports this relationship between firearm availability and homicide rates, although these earlier studies were not as well controlled.[31,32]

Internationally, the presence of guns also appears to be a fatal risk factor. The Swiss researcher Killias found that when homicide and suicide rates in various western countries are compared with levels of gun ownership, a consistently significant correlation is evident between the number of households with guns and the rates of homicide with a gun, of suicide with a gun, and the overall rates of homicide or suicide by any means.[22] No significant correlation existed between gun ownership and the rate of homicide by means other than a gun. Killias found the rate of homicide from firearms alone in the United States was 44.6 homicides per million residents. Except for Northern Ireland with 35.5 homicides per million, the rate of homicide due to firearms was over five times lower in all other countries. Other international comparisons indicate that the United States is a more violent and deadly place for young men than anywhere else in the western world, almost entirely as a result of homicides involving firearms.[10]

These international studies are not case-controlled, but they do represent comparisons among countries that share many social and economic similarities. In addition, Killias's study showed no statistically significant correlation between the rate of firearm ownership and non–firearm-related homicides and suicides,[22] indicating that countries with higher rates of gun ownership are not necessarily inherently more violent or suicidal. In fact, if firearms were excluded as a cause of homicide, the differences between the rates of homicide in the United States and other countries would decrease by 70% to 90%.[10]

Gun Policy Objectives

In terms of broad policy objectives that address guns themselves, essentially two directions exist: actively or passively allow the supply of guns to increase, or decrease the supply of guns. From the data, decreasing the number of firearms appears to make the most sense in stemming the rising problem of gun violence. But what, specifically, can be done to decrease firearms in California? Before such a question can be answered, the current status of legal issues surrounding levels of firearm availability should be understood.

Federal Law and the Second Amendment

The Second Amendment to the US Constitution states, "A well-regulated militia being necessary to the security of a free State, the right of people to keep and bear arms shall not be infringed." The Second Amendment was written to ensure the states' ability to raise well-regulated militias, so although Congress's power to tamper with gun regulation is limited, the individual states have relative freedom to pass laws with regard to firearms.[33] As written in the Supreme Court case *Presser v Illinois* in 1885, "The Second Amendment to the Constitution is a limitation only upon the power of Congress and the national government, not upon that of the states" (116 US 252 [1886]).

California Law

In recent years, the California legislature has passed several laws related to firearms. Examples are classified here using a typology similar to that developed by firearm policy experts[21,26]:

- The manufacture and sale of 55 assault weapons were banned.
- Obstacles to firearm availability have been increased, including a 15-day waiting period on firearm purchases and a limitation on private gun sales by unlicensed sellers.
- Laws have addressed user behavior and gun allocation, including increased restrictions on firearm ownership by convicted felons, prohibited sale to persons under restraining order for domestic violence, penalties to those possessing firearms while under the influence of illegal narcotics, stricter penalties for persons illegally carrying firearms in public, and handgun safety training requirements.
- Other measures have attempted to regulate the lethality of the product itself, including a ban on multiburst trigger activators.

Many other similarly focused proposals are currently under consideration by the legislature.

Although these laws, and many of the more than 20,000 laws in force nationwide[34] begin to address the gun issue, the logistics of enforcement are difficult, and evidence of efficacy is questionable. For example, because the ban on assault weapons restricts certain weapons only by name, manufacturers can simply change the name of a banned weapon, perhaps with some cosmetic modifications, and then legally offer the "new" weapon for sale. For the other laws, the absence of a mechanism to account for existing firearms or for illegal users such as felons or domestic abuse suspects makes eliminating illegal sales difficult and the effectiveness of waiting periods uncertain.

Another law, however, represents a new tack in the fight against irresponsible firearm behavior—liability. In 1991, it became a crime in California to leave a loaded firearm where a child could obtain and use it to injure someone. The idea that owners must take greater responsibility for their weapons seems to be taking hold among many policy makers.

In terms of local legislation, little can be done in California, largely because communities cannot pass local laws that affect the licensing or registration of firearms. Because of state preemption law, last amended in 1971, such matters are reserved for statewide action only, exclusive of all attempts at local regulation (Cal Code §53071).

Thus, even if a community decides that the state has been ineffective in curbing firearm violence, that community cannot pass gun measures that involve licensing or registration.

Ideas for Addressing Gun-Related Violence

Policy Analysts' Proposals

Several leading firearm policy analysts have made proposals that address gun-related violence. They have recommended increasing data collection to better understand firearm violence and to evaluate the efficacy of prevention interventions. They stress the importance of educating policy makers, attorneys, physicians, consumer advocacy groups, and the public as to the inherent dangers of firearms and to the firearm industry's use of fear to sell these dangerous "solutions."[26] Others have analyzed the shortcomings of existing legislative approaches.[21]

Other Proposals

The following policy suggestions are based on the legal, scientific, and statistical information discussed earlier. These policies focus on firearms themselves, but other policies regarding such issues as modification of violent behavior, control of substance abuse, enhanced law enforcement, and economic improvement are important as well.

- *Allow local governments and communities to participate in the effort to decrease firearm violence and to address a growing health concern.* California's preemption law denies citizens the ability to address this growing health problem. Allowing local governments to have a greater degree of regulatory power over the sale, possession, and use of firearms is a necessary step toward alleviating the hazard of guns. A single community taking action to regulate firearms will not solve the problem of gun violence, and there is a role for state-level action, but local activity can serve as a model to encourage similar action by other communities and can send a strong signal to a state legislature.
- *Create a state agency, with members representing a diversity of backgrounds, to serve as an expert body for evaluating new weapons in the spirit of existing law.* New weapons would need to be inspected for characteristics similar to those guns restricted by law. This body could also serve as a source of balanced information regarding firearms. In such a forum, studies and statistics could be scrutinized thoroughly for proper methodology and accuracy, and recommendations could be made regarding the costs and benefits of certain weapons to society. For example, given their use in over 60% of homicides, handguns might be a logical subject of analysis.

This group could be housed within the Department of Health, giving increased attention to gun violence as a public health problem. The nature of gun violence has become clearer. Guns need to be seen as more than the tools of hardened criminals. New perspectives in thinking about the subject are needed from not only the justice system, but also from a health system viewpoint.

- *Increase owner, dealer, distributor, and manufacturer accountability through the creation and enforcement of a legal standard for safeguarding firearms in storage or in transit and through stricter liability for illegal sales and unsafe loaning of firearms.* Gun advocates have repeatedly called for more responsible behavior among gun owners, saying that people, not guns, are the real cause of firearm fatalities and injury. Because most guns used in crimes are stolen from individual owners, standards of reasonable storage should be established to ensure that the power gun owners have purchased does not fall easily into the hands of unlawful persons. Breach of this standard would result in fines and some loss of ownership privileges. In addition to the effects these actions would have on criminal access to guns, well-secured household guns are likely to be less dangerous to children and to the large number of potential victims of domestic, heat-of-the-moment assaults.

Owners who sell their guns to others without completing legally required paperwork and those who temporarily loan their guns to illegal users should be held strictly liable for any damage that occurs while the gun is used by these other persons. The standards for dealers, distributors, and manufacturers would be proportionally stricter and the punishments for breach of these standards relatively more severe, given the larger quantities of firearms that their shops, transport vehicles, and warehouses hold.

Teret and Wintemute have also called for direct accountability from firearm manufacturers. They claim that because of the increasingly evident association between the presence of firearms and the incidence of firearm morbidity and mortality, firearm manufacturers, like manufacturers in other industries, should be liable for the damages that their products cause.[35]

- *Establish a firearm registry to increase the enforcement and efficacy of current and proposed laws, to increase safety education, and to improve the understanding of criminal and noncriminal firearms violence.* Koop and Lundberg have compared the need for firearm registration with the current benefits of automobile registration, especially as firearm deaths are beginning to outnumber those caused by motor vehicle accidents in states such as Texas and California.[36] Registration of firearms and firearm users, with annual registration fees, is crucial to any law that hopes to limit illegal sales or increase owner liability and is necessary for a clearer understanding of gun violence.

Firearm users should obtain operating permits from law enforcement agencies, and those permits should be suspended for unlawful activity. Such registration would facilitate background checks of potential purchasers and facilitate the exclusion of illegal purchasers. In addition, all guns manufactured in or legally shipped to a state could be entered into a registry and tracked, making manufacturers, distributors, and dealers more accountable for the dissemination of the guns they produce, transport, and sell.

An annual registration fee for firearms is also crucial in increasing owner accountability. Illegal private sales and transfers by gun owners would be made less attractive be-

cause the annual registration fee could not be avoided until owners presented to an official agency for transfer of gun ownership. Registration would also allow enforcement of the recommended laws outlined here, because owners whose weapons were stolen would similarly continue to pay registration fees until reporting their theft. Failure to report the sale or theft of a registered firearm would be risky, given the possibility that the gun might be used unlawfully in the future, recovered, and then easily traced through the registry to its original owner.

In addition to these deterrent effects, registration would still protect the rights of legally registered gun owners. For example, hunters could still loan guns to friends, as long as those friends held current operator's permits. Registration would also create a better means for law-abiding citizens to ensure that the guns they sell fall into the hands of similarly lawful users.

Registration as well as a comprehensive database of firearm injuries and violence would help in the gathering of better information in an industry that is essentially untouched by any functional regulation. A much more comprehensive understanding of the nature of gun violence is needed, including increased identification of the risks and benefits of gun ownership, a clearer picture of the pathway of guns from manufacturer to criminal, and a truer understanding of the types of guns and gun users most likely to be involved in firearm violence.

Realistically, those wishing to bypass registration might go to nearby states to purchase their guns. A system in California, however, could serve as a model for other states wishing to enact their own registration systems, which could be compatible and accessible across state lines. The operation of such systems could be financed at least partially through the collection of registration and permit fees. Although this approach might appear burdensome and bureaucratic, it seems only logical that, with their increasingly negative effect on society, guns should be monitored and studied at least as well as automobiles.

Taken together, these four policies would give citizens power on a community level, help decrease the steady introduction of the least beneficial and most dangerous weapons, decrease the easy flow of weapons to criminals, poorly experienced gun handlers, and unstable persons, create safer home environments, and allow for a gradual and comfortable de-escalation of the growing problem of gun violence. Law-abiding citizens would still have access to the guns they enjoy, but with the requirement that they take greater responsibility for their guns. Even these indirect measures will likely be met with extreme distrust and skepticism from gun advocates, however.

Gun Advocates' Proposals

Many gun owners fear registration and other types of regulation, expressing concern over "police-state policy." A memo from the National Rifle Association (NRA) attacks the Federal Bureau of Investigation's new gun regulation policy proposals as beyond the purview of the Bureau, repugnant to American freedoms, and an ominous sign of police state tactics against law-abiding gun owners (W. R. LaPierre, J. J. Baker, "FBI Director Launches Police State Agenda Against Law-Abiding Gun Owners" [Memo], *American Rifleman*, August, 1993, p 58).

Although claiming to be afraid of a police state, this group often states that the real solution is to give increased power to law enforcement and the justice system. As the Director of Federal Affairs for the NRA stated in testimony on two bills before the Senate Judiciary Committee Hearing on Assault Weapons: "The NRA has repeatedly suggested ways in which [effective crime deterrence] can be accomplished, including mandatory sentences without parole, more prosecutors, more prisons, and an end to plea bargaining" (US Senate Judiciary Committee, Assault Weapons Ban, August 3, 1993).

There is a place for stricter law enforcement as a means of decreasing violence, but such a policy, by itself, has been ineffective. Over the past decade, the rate of spending on California's corrections system increased more than that on education, health, welfare, or transportation, and the number of prisons in California more than doubled from 12 to 26 (M. Taylor, "Aging Inmates—A Growing Prison Presence," *San Francisco Chronicle*, August 2, 1993, p A1).

Total expenditures for operating California's justice system nearly doubled between 1985 and 1991, not including building construction costs or the cost of regulatory agencies.[18] In addition, the justice system workforce increased from 115,091 to 150,737 workers between 1985 and 1991, which equates to a rate of increase twice that of California's population growth during this period.[18] Corrections officers and sworn law enforcement personnel such as prison guards and police officers accounted for 73% of all new personnel additions. Still, the rate of firearm-related and other violence continues to grow.

Thus, to reduce firearm violence in the manner proposed by many gun advocates, the justice system will either have to grow even more rapidly or change in its fundamental operation, or both. In the process, as the justice and legal systems gain increasing money and power, the public may have to accept escalating police power, decreasing personal privacy, compromise of the right to due process of law, and an effective decrease in personal freedoms. Ironically, although gun advocates may believe that gun regulation is tantamount to creating a police state, their proposals for decreasing violence solely through increased law enforcement seem to lead to a more serious and much broader type of police state.

Conclusion

As a leader in firearm violence, California has begun to pass firearm legislation. Many of these laws may delay access, but they do not prevent it. They may dictate change, but they cannot enforce it. Waiting periods, stricter punishment, limiting private sales, and prohibiting certain sales send an important message, but do not constitute a comprehensive plan.

The problem of gun violence in California cannot be solved with a sudden and dramatic stroke of legislative action.

Guns are an important factor in gun violence, but they are not the only factor. Dealing with the large supply of

guns that already exists will be a challenge. Yet, the complexity of firearm violence is not an excuse for the continued reckless additions to an ever-expanding public arsenal.

We as a society have choices. We can allow the supply of guns to increase, or we can attempt to curb their growth. We can ask those who possess and manufacture guns to take greater responsibility for the damage that they create, or we can continue to deny the destructive element that the presence of guns creates in our communities. The evidence is increasingly clear—guns do not protect life, they destroy it. The time has come to protect life, not guns.

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Articles

Physician Management of Hypercholesterolemia

A Randomized Trial of Continuing Medical Education

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To determine the effect of continuing medical education (CME) on compliance with the recommendations of the National Cholesterol Education Program Expert Panel on high serum cholesterol levels in adults, we randomly assigned primary care physicians in 174 practices to 3 groups, 2 that underwent either standard or intensive CME and a control group. The standard CME group was offered a free 3-hour seminar on high serum cholesterol levels; the intensive CME group was offered in addition follow-up seminars and free office materials. After 18 months, we audited 13,099 medical records from the 140 practices that remained in the study. There were no significant differences ($P > .15$) in screening for high serum cholesterol or compliance with guidelines between the groups receiving continuing medical education (51% screening; 33% compliance) and the control group (57% screening; 37% compliance). In the prespecified subgroup of patients with hypercholesterolemia, there was a trend toward a modest benefit from the continuing medical education interventions: compliance was 21% in the control group, 23% in the standard CME group, and 27% in the intensive CME group ($P = .07$ overall). These results emphasize the need for better ways to change behavior in practicing physicians and the importance of studying the implementation of preventive health recommendations.

(Browner WS, Baron RB, Solkowitz S, Adler LJ, Gullion DS: Physician management of hypercholesterolemia—A randomized trial of continuing medical education. West J Med 1994; 161:572-578)

Continuing medical education (CME) is the third and final phase of medical education. Physicians participate in CME to update their medical knowledge, to improve their medical practice, and in many states, to maintain their medical license. Despite the enormous expenditure of time and resources—about $3 billion a year in the United States—the efficacy of CME on physician performance and health outcomes is not certain; studies have demonstrated mixed results.[1-6]

There are several problems in evaluating the efficacy of CME. Physicians may have only a relatively few patients with some conditions, making it difficult to demonstrate changes in patient outcome. For more common conditions, physicians may have already developed a complex style of practice that can be difficult to change. Many physicians are already functioning at a high level, which makes demonstrating improvements difficult. Finally, most studies have assessed the effects of CME in groups of residents, physicians in health maintenance organizations, or in volunteer physicians, often with recruitment rates of 10% or less, limiting the ability to generalize results to community physicians.[2,7-10]

We therefore chose to evaluate the efficacy of CME in improving the management of high serum cholesterol levels by non–university-affiliated physicians in private practice. Guidelines for screening and management were developed by the National Cholesterol Education Program (NCEP) and published in 1988.[11] They have since been widely disseminated, but not as yet widely adopted in practice.[12,13] Most physicians do not have extensive experience treating patients with high serum cholesterol levels, and the recent public interest in the topic has made physicians eager to improve their knowledge and management skills.[14,15]

Our specific aim was to determine whether randomly assigning primary care physicians in private practice to receive CME, with or without intensive follow-up, about the detection and treatment of high serum cholesterol levels would result in better management of patients compared with the patients of a control group of physicians.

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At the time this study was being investigated and prepared for publication, the lead author (W.S.B.) was an employee of the federal government. It therefore fits the description in the United States Copyright Act of 1976 of a "US government work" and cannot be copyrighted.

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ABBREVIATIONS USED IN TEXT

CI = confidence interval
CME = continuing medical education
HDL = high-density lipoprotein
LDL = low-density lipoprotein
NCEP = National Cholesterol Education Program

Methods

Participants

The recruitment of physician practices was carried out between September 1988 and March 1990. Lists of possible participants from the east San Francisco Bay Area (Contra Costa, Solano, and Alameda counties excluding Berkeley) were drawn from local medical societies, hospital rosters, and medical building directories. Private or small group (3 or fewer physicians) practices in internal medicine, family practice, or general practice were screened for three criteria: adult primary care making up at least 50% of the practice, accepting new patients, and planning to remain in the current area through 1991. Physicians were contacted by a letter stating that we were conducting a study of CME and cholesterol management, then by a follow-up phone call, and finally by a visit by a member of our staff. We enrolled 197 physicians (in 174 practices) out of 302 contacted, for an overall recruitment rate of 65%. Of the total, 16 (8%) were women and 50 (25%) were members of ethnic minority groups (29 Asian, 14 African American, and 7 Hispanic). Of those who declined to enroll, the most common reasons given for refusal were "lack of time" and "unwilling to participate in research."

Physician practices were randomly assigned (using an off-site computer-generated list) to either a control group (n = 62 practices), a standard-CME group (n = 55 practices), or an intensive-CME group (n = 57 practices). The proportions of women and of minorities were similar in the three groups.

Interventions

Members of the control group received a letter shortly after recruitment explaining that they had been randomly assigned to the control group and that they would be entitled to attend a seminar on hypercholesterolemia and receive our packet of educational materials in about 18 months, after completion of the study. Thereafter, they received no contact until the chart review.

The educational interventions for the standard-CME group and for the intensive-CME group began in October 1988 and were completed in May 1990, before the recent controversy about the appropriateness of some of the NCEP recommendations.[16,17] Both groups were invited to attend a three-hour free CME seminar on "Appropriate Management of Hypercholesterolemia" for which they received three hours of educational credit. As much as possible, the seminars followed the format of usual CME activities. Each seminar provided extensive instruction on the scientific background for the NCEP guidelines, the guidelines themselves, patient counseling techniques, dietary recommendations, and drug therapy. Seminars were held at convenient times and locations in small groups of 10 to 20 physicians, and low-fat, low-cholesterol meals were served. A syllabus was provided, which was mailed to those who failed to attend one of several scheduled seminars. Following completion of the seminar, the standard-CME group received no contact until the chart review.

In addition to the seminar, the intensive-CME group was offered supplemental educational materials, office visits, and follow-up seminars. A staff member visited the office to explain the use of the following free educational materials:

- The book, *Eater's Choice*, which was given to all physicians.[18] They were encouraged to read and use the system outlined in the book for themselves as well as for their patients.
- A patient manual entitled "A Change of Heart." The manual emphasized a positive attitude, behavioral aspects of lifestyle change, goal setting, ways to reduce dietary saturated fat and cholesterol, the importance of reading food labels, and rewards for goals reached. Refrigerator magnets with the "Change of Heart" logo for displaying the food charts in the patient manual and pocket-sized food tables showing calorie and saturated-fat content for common foods were included. These were used by physicians in 79% of the practices.
- A seven-minute companion videotape, also called "A Change of Heart," emphasizing a positive attitude, humor, heart-healthy grocery shopping, and the importance of screening. One tape was provided to each physician, to be loaned to patients or viewed in the office. This was used by physicians in 43% of the practices.
- Table tents for office display as a reminder to patients to ask for a cholesterol test and to view the videotape. These were used by physicians in 19% of practices.
- Pocket-sized laminated cards and larger, blotter-sized versions of the cholesterol management algorithms containing the guidelines issued by the NCEP. These were used by physicians in 33% of practices.
- Postcard reminders for use by physicians to bring patients to the office for a cholesterol test. These were used by physicians in 7% of practices.
- Chart reminder "post-its" for physicians to use in patients' records as a prompt to check for cholesterol screening, diet counseling, or drug therapy. These were used by physicians in 9% of practices.

A month after the office visit, physicians attended a two-hour follow-up seminar. Case histories were presented, and treatment guidelines were reviewed. Physicians were also reminded about the use of the educational materials and asked for their evaluations of the materials. A staff member also visited physicians' offices to meet with the staff and to explain the physician's participation in the project and the use of educational materials. Physicians also received encouraging phone calls from the project staff and a letter with recent journal articles. A

month later, physicians received a second office visit by a staff member, and a free general medical book—*Current Medical Diagnosis and Treatment*—was provided.[19] The use of educational materials was reinforced, and physicians were asked for additional comments. Two to three months later, physicians were invited to attend a third education session to review treatment guidelines, answer questions that had arisen, and discuss new information when appropriate. Following this seminar, the physicians received no contact until the chart review, although many continued to contact project staff with clinical questions or requests for additional materials.

Chart Review

A year and a half after randomization, we reviewed the medical records of as many as 100 randomly selected patients per practice to determine compliance with NCEP recommendations and to measure the effectiveness of the educational methods. The chart abstractors used prepared lists of random numbers to select records for audit. Different lists were provided for different practice sizes. If the selected medical record met eligibility criteria for review, it was audited; if not, the next record was selected. Medical records were eligible for review if all of the following criteria were met:

- At least one visit was made to the practice in the previous 18 months.
- Patient was between the ages of 20 and 70 years.
- No disease existed that would preclude the need for screening (such as the acquired immunodeficiency syndrome, chronic pulmonary disease requiring oxygen, metastatic cancer, or dementia).

Medical records were audited in physicians' offices by two full-time chart abstractors who were blinded to the physicians' group assignments and used standardized data collection forms. We ascertained a patient's age and sex; all total cholesterol, triglyceride, and high-density lipoprotein (HDL)-cholesterol measurements (with dates); and the use of dietary recommendations and drug therapy for at least the previous five years. In addition, we reviewed records for known or suspected coronary artery disease, by searching for phrases such as "myocardial infarction", "ischemic heart disease," "possible angina," and "positive stress test." We also recorded the presence or absence of the following risk factors: male sex, history of hypertension or blood pressure higher than 140/90 mm of mercury, current smoking of at least ten cigarettes per day, diabetes mellitus, obesity, peripheral vascular or cerebrovascular disease, and an HDL-cholesterol level of 35 mg per dl (0.90 mmol per liter) or lower, based on NCEP criteria.[11] All patients with coronary artery disease or with two or more cardiac risk factors were classified as "high risk."

A research assistant reviewed each data collection form. All patients with average total cholesterol levels of greater than 240 mg per dl (>6.20 mmol per liter) or greater than 200 mg per dl (> 5.15 mmol per liter) if high risk, any with cholesterol measurements of greater than 300 mg per dl (>7.75 mmol per liter), or patients who were taking cholesterol-lowering medications (a total of 1,718 patients) were referred for blinded review by three physicians to determine compliance with NCEP guidelines.[11] Our interpretation of the guidelines allowed physicians some discretion in management, especially for the frequency of follow-up in adequately controlled cases (discussed later). The three physician-investigators met and discussed each of these 1,718 cases; disagreements were resolved by consensus in all instances.

The management of all patients was classified as compliant with NCEP recommendations or not. Compliance with recommendations required as many as three steps:

- *Screening for total cholesterol.* All patients must have had at least one total cholesterol level measured within the past five years. If the most recent (or the average, whichever was lower) cholesterol level was less than 240 mg per dl (< 6.20 mmol per liter) or less than 200 mg per dl (< 5.15 mmol per liter) if high risk, and the patient was not on any pharmacologic therapy for hypercholesterolemia, then management was compliant. If the patient had not been screened for a high serum cholesterol level, then management was not compliant.
- *Determination of low-density lipoprotein (LDL)-cholesterol level.* If the initial cholesterol level was 240 mg per dl or higher (≥ 6.20 mmol per liter) or 200 mg per dl or higher (≥ 5.15 mmol per liter) if high risk, at least one determination of LDL-cholesterol level was required. If the most recent (or the average, whichever was lower) LDL-cholesterol level was less than 160 mg per dl (<4.15 mmol per liter) or less than 130 mg per dl (< 3.35 mmol per liter) if high risk, management was compliant. If the patient had an LDL-cholesterol of greater than 160 mg per dl (> 130 mg per dl if high risk) and was not on any therapy for hypercholesterolemia, the management was not compliant. We did not require annual LDL-cholesterol measurements in those with an initial LDL-cholesterol level of less than 160 mg per dl (< 130 mg per dl if high risk).
- *Treatment of elevated LDL-cholesterol level.* All patients with an LDL-cholesterol level of 160 mg per dl or higher (130 mg per dl if high risk) (≥4.15 mmol per liter [3.35 mmol per liter]) should have had a three- to six-month trial of a cholesterol-lowering diet. We allowed physicians to use drug treatment without a diet trial if the LDL-cholesterol level was 220 (high risk, 190) mg per dl or higher (≥5.70 [5.00] mmol per liter). Pharmacologic intervention was required in those with LDL-cholesterol levels of 190 (160) mg per dl or higher (≥5.00 [4.15] mmol per liter) despite a diet trial, with a therapeutic goal of an LDL-cholesterol level of less than 160 (130) mg per dl (<4.15 [3.35] mmol per liter). The institution of pharmacologic therapy required that at least two LDL-cholesterol determinations had been done, with an average level of 190 (160) mg per dl or higher (≥5.70 [5.00] mmol per liter); otherwise, management was not compliant. In this last situation, we did not consider psyllium a pharmacologic agent.

If the LDL-cholesterol goal was not met within six months, compliance required that the physicians make an appropriate change in therapy—for example, instituting a stricter diet, adding a medication to an unsuccessful dietary regimen, increasing a medication dosage, or changing medications—at least every three months. Management was considered compliant if the LDL-cholesterol level was high, but the physician was attempting or planning to attempt to lower it. We required checking an LDL-cholesterol level annually in patients while they were on pharmacologic therapy.

The following situations that did not meet these criteria were allowed as compliant management:

- The patient was screened for hypercholesterolemia during the final three months of the abstract period (or if the first elevated cholesterol level was detected then).
- The patient was being treated successfully (with diet or drugs) for a high LDL-cholesterol level to achieve a level of less than 130 (high risk, 160) mg per dl (< 3.35 [4.15] mmol per liter) at the time he or she became a patient in that practice.
- The patient refused further follow-up for high serum cholesterol levels, and that refusal was noted in the chart.
- The patient had at least two measurements of HDL-cholesterol and triglyceride levels that were stable. In these cases, we allowed the use of the total cholesterol level as an LDL-cholesterol surrogate for follow-up.

The primary outcome variable was the proportion of patients in a practice whose management complied with NCEP guidelines. Prespecified secondary outcome variables were the proportion of all patients in a practice who were screened for high serum cholesterol levels and the proportion of those with an initial cholesterol level that was high (≥ 240 mg per dl [≥ 6.20 mmol per liter] or ≥ 200 mg per dl [5.15 mmol per liter] if high risk) whose management was compliant with guidelines.

Statistical Analysis

We compared the overall proportions of patients whose management complied with guidelines, the proportions of patients screened for hypercholesterolemia, and the proportions of patients with elevated cholesterol levels whose subsequent management was compliant, using techniques that adjust for the effect of cluster sampling.[20] These techniques take into account that physicians' practices, not patients, were the units of randomization, but that patients were the units of analysis. They allow the determination of adjusted χ^2 values and confidence intervals. We compared physician characteristics using χ^2 or Fisher's exact test. The primary comparisons were between the intervention groups and the control group; we also compared the two intervention groups with each other. Statistical significance was set at a two-sided $P < .05$. We did not adjust for multiple comparisons.[21]

Results

Of the 174 practices that were initially randomized, 34 (20%) were lost to follow-up (Table 1). There were no significant differences in the proportion lost to follow-up (either total or cause-specific) in the three groups (all $P > .25$). All reported analyses are based on the 13,099 patients in the remaining 140 practices (48 in the control group, 45 in the standard-CME group, and 47 in the intensive-CME group), which included a total of 168 physicians. Of this total, 13 (8%) were women, and 43 (26%) were members of minority groups (28 Asian or Middle Eastern, 13 African American, and 2 Hispanic); there were no significant differences in the proportion of women and of minorities in the three groups. Of the 140 practices, 83% had at least 90 eligible patients, and 91% had at least 70 eligible patients.

TABLE 1.—*Reasons Why Physician Practices Did Not Participate in Study, by Randomized Group*

Reason for Exclusion	Randomized Group, No. Control (n=62)	Standard CME (n=55)	Intensive CME (n=57)
Ineligible*	0	1	1
Died	1	0	1
Moved	5	3	3
Retired, changed practice	4	1	1
Refused chart audit	4	4	3
<40 Eligible patients	0	1	1

CME = continuing medical education

*Two practices were determined to be ineligible at the time of chart review because they did not do primary care.

Physicians from 38 (84%) of the 45 standard-CME practices and 42 (89%) of the 47 intensive-CME practices attended the initial seminar; the percentages attending the two follow-up sessions for the intensive-CME group were 79% (37 of 47) and 55% (26 of 47), respectively.

The age, sex, and risk status of the 13,099 patients were similar in the three groups of practices (Table 2). Overall, 58% of the patients were women, and 52% were older than 55 years. About 28% of patients had coronary artery disease or were at high risk of coronary artery disease. There were no statistically significant differences in patient characteristics in analyses that adjusted for the effects of clustering.

Compliance With National Cholesterol Education Program Guidelines

More than half of all patients had been screened for high serum cholesterol levels, and about one in three patients were managed in compliance with the NCEP recommendations (Table 3). Although overall compliance rates were 3% to 4% higher in the control group than in the CME groups, there were no significant differences between the groups. The 95% confidence interval (CI) for the difference between the standard-CME group and the control group, for example, was from −10% to +2%. Screening rates were higher, but not statistically so, in the control group, with a 95% CI for the difference between the CME and control groups of −14% to +2%.

Of the 4,536 patients whose management was considered in compliance, 3,782 (83%) had acceptable screening cholesterol levels (< 240 mg per dl [< 6.20 mmol per

TABLE 2.—*Characteristics of Patients, by Group**

Patient Characteristic	Control (n=4,491) No. (%)	Standard CME (n=4,157) No. (%)	Intensive CME (n=4,451) No. (%)
Female sex	2,505 (55.8)	2,423 (58.3)	2,613 (58.7)
Age, years†	46.6 ± 14.1	46.4 ± 13.9	47.2 ± 14.1
High risk‡	1,232 (27.4)	1,146 (27.6)	1,317 (29.6)

CME = continuing medical education

*Data on sex were missing for 8 patients (5 control, 2 standard CME, and 1 intensive CME). Data on age were missing for 1,076 patients (360 control, 324 standard CME, and 392 intensive CME).

†± 1 standard deviation.

‡Patients with known or suspected coronary artery disease or with two or more cardiac risk factors were considered at high risk.

liter] or 200 mg per dl [5.15 mmol per liter] if high risk). These patients required no additional management. When the analysis was restricted to the prespecified subgroup of patients who had a screening cholesterol level that was high (≥ 240 mg per dl, [≥ 6.20 mmol per liter] or 200 mg per dl [5.15 mmol per liter] if high risk), about one in four of these patients was managed in compliance with NCEP guidelines (Table 3). There was a trend toward better compliance ($P = .07$) in the two CME groups. Compliance rates were 6% higher (95% CI, +1% to +11%; $P = .02$) in the intensive-CME group than in the control group.

Among the 2,426 patients who were found to have elevated cholesterol levels (≥ 200 mg per dl if high risk, or ≥ 240 mg per dl, otherwise) the most common errors in subsequent management were failure to measure an LDL-cholesterol level (n = 806; 33%) and failure to institute treatment if the LDL-cholesterol level was elevated (n = 450; 19%). There were no differences in the frequencies of these errors in the three groups ($P > .10$).

There were no differences between practices in the two CME groups in overall compliance ($P > .90$), screening ($P > .90$), or compliance among patients with high cholesterol levels ($P = .22$).

Wide variations were seen in practice patterns in all three groups. For example, the proportion of patients who were screened for high serum cholesterol levels in the control practices ranged from a low of 12% to a high of 93%; the same two practices achieved overall compliance rates of 5% and 65%, respectively. Although one practice in the intensive-CME group achieved an overall 90% compliance rate and a 57% compliance rate (17 of 30) in patients with high cholesterol levels, another practice had an overall compliance rate of 10% and failed to manage a single patient (of 10 such patients) with an elevated cholesterol level in compliance with NCEP recommendations.

Comment

Our results indicate that continuing medical education for physicians, even when combined with intensive follow-up and office-based educational materials, did not elicit overall compliance with the NCEP expert panel's recommendations on the detection, evaluation, and treatment of hypercholesterolemia. About half of the 13,099 patients had not been screened for high serum cholesterol levels, and overall rates of compliance were between 33% and 37%, making it unlikely that we failed to detect an effect because levels of screening and management compliance were already high. We found no differences between the performances of practices assigned to the standard-CME group and the control group. A modest benefit of the intensive-CME intervention on compliance with recommended management was seen in the predefined subgroup of patients with elevated cholesterol levels who required more than a simple screening test.

We did not anticipate the trends that we observed toward higher screening and compliance rates in the control group and think that chance is the most likely explanation for these results. Another possibility is that the intervention-physicians were more aware of the complexity of the management process, and this discouraged them from screening some patients. Once screening was initiated, however, the intervention-physicians were somewhat more likely to manage those found to have elevated cholesterol levels according to guidelines. The net effect is that the (unknown) proportion of all patients with high cholesterol levels whose management met NCEP guidelines was probably similar in the three groups. The actual proportions are not known because cholesterol levels are missing, of course, for those who were not screened.

One of the strengths of this study is the representativeness of the participating physicians and their patients. The sample includes members from several ethnic groups whose practices are in a variety of socioeconomic circumstances in urban, suburban, and semirural areas of the San Francisco Bay Area. All were self-identified primary care providers. They were not selected on the basis of affiliation with an academic medical center. Our recruitment rate of nearly two thirds of all physicians contacted is high. These differences between our sample and those in other studies of continuing medical education, which have mainly enrolled residents, clinical faculty, or members of a health maintenance organization, often with

TABLE 3.—*Patients Screened for Hypercholesterolemia and Those Whose Management Complied With Recommendations of the National Cholesterol Education Program (NCEP), by Group*

Patient Characteristic	Control No. (%)	Standard CME No. (%)	Intensive CME No. (%)	P* Value
Patients, No.	4,491	4,159	4,451	
Screened	2,548 (57)	2,135 (51)	2,278 (51)	>.25
Compliant with NCEP	1,659 (37)	1,377 (33)	1,500 (34)	>.25
Cholesterol levels high, No.†	1,125	991	1,064	
Compliant with NCEP	236 (21)	232 (23)	286 (27)	.07

CME = continuing medical education

*All analyses adjusted for the effects of clustering by practice (see Methods).

†Screening cholesterol level ≥240 mg/dl (≥200 mg/dl if high risk) (620 mmol/liter [5.15 mmol/liter if high risk]).

much lower recruitment rates, may explain why we were unable to show an overall benefit. On the other hand, others have also found relatively low rates of treatment of patients with elevated cholesterol levels, similar to those we observed.[12,14,22] Given the recent study showing that women physicians are more likely to perform preventive services than their male counterparts,[23] it is unfortunate that our sample included only 13 women physicians, reflecting the small proportion of women in the practices that composed our sampling frame.

In our study, physician practices, not patients, were the unit of randomization and are thus the appropriate unit of analysis. Had we failed to account for the effects of clustering within practices, we would have erroneously concluded that screening for high serum cholesterol levels (unadjusted χ^2 2 degrees of freedom [*df*] = 35.48, $P < .0001$) and compliance with recommendations (unadjusted χ^2 2*df* = 16.45, $P < .001$) were more common in the control practices.

This study has several limitations. Not all physicians who were randomly assigned to the CME groups took advantage of all the interventions that we offered, and not all physicians who were originally randomly selected remained in the study. Despite our best efforts to identify physicians in stable practice settings, during the time of our study (from 1988 to 1991), there was great turmoil in medical practice in the San Francisco Bay Area; many physicians retired, moved, or changed practices. Others refused to allow chart audit. Although the proportion of physicians who were lost to follow-up was similar in the three groups, we cannot eliminate the possibility of differential loss to follow-up. That physicians in the CME groups whose management of hypercholesterolemia complied with NCEP recommendations would have been more likely to drop out than those in the control group seems unlikely.

We assumed that physicians do not remember management plans for individual patients unless they are written in the medical record. Thus, we may have underestimated the use of diet therapy, for example, if a physician failed to note it. On the other hand, we may have overestimated the use of diet counseling if a physician recorded doing so, but actually did not give such counseling—or did so ineffectively. We also may have overestimated screening rates because some of the cholesterol levels may have been ordered as part of a routine chemistry panel. In addition, longer follow-up would have resulted in a higher prevalence of screening in all three groups. Because most of the compliance with guidelines occurred by screening patients with normal cholesterol levels, overall compliance would likely also be higher. Because all auditing was done blinded to group assignment, these limitations would not affect the between-group comparisons, however.

The determination of compliance was based on NCEP guidelines, using a "benefit of the doubt" approach. These guidelines are complex, requiring several diagnostic and treatment steps.[11,24] Our results suggest that despite extensive educational efforts, the NCEP guidelines may be too cumbersome for many practitioners. Even given the possible benefit of the intensive-CME intervention among patients with high cholesterol levels, management was not in compliance with NCEP recommendations in more than three quarters of the patients in that group. This emphasizes the importance of determining the applicability of clinical guidelines before they are widely disseminated.[25] It would be of great interest to know whether a less complicated strategy would have greater applicability and more widespread public health effects.

The limitations of the standard-CME lecture format—in terms of demonstrating effects on patient care—are well-recognized.[4] Our study confirms those results, as well as those suggesting that physician-oriented approaches to preventive services may not be efficacious.[26] The results seem to suggest that programs that include more intensive education with enabling factors (such as patient handouts) and reinforcement (such as follow-up seminars) may modestly improve patient care, at least in the subgroup of patients who require more management. We are unable to determine which aspects of our intensive intervention were responsible for the possible benefit that we observed.

Given the substantial controversy that has arisen about the wisdom of screening and treating high cholesterol levels in many adults,[16,17] we cannot say whether the relatively low levels of compliance with the NCEP recommendations that we observed were good or bad. We can say that CME was not particularly effective in improving compliance with those guidelines among non–university-affiliated community physicians who practice primary care. That our results will apply to subsequent modifications of the NCEP guidelines[24] and perhaps to other expert guidelines seems likely. These results emphasize the need for better ways to change behavior in practicing physicians and the importance of studying the implementation of preventive health recommendations.

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Conferences and Reviews

Antibiotic Therapy for Ocular Infection

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Infections of the eye can rapidly damage important functional structures and lead to permanent vision loss or blindness. Broad-spectrum antibiotics should be administered to the appropriate site of infection as soon as a diagnosis is made. Topical drops are preferred for corneal and conjunctival infections. Intravitreal antibiotics, and possibly subconjunctival and parenteral antibiotics, are preferred for endophthalmitis. Parenteral antibiotics are recommended for infection in deep adnexal structures. We review specific aspects of antibiotic therapy for ocular and periocular infection.

(Snyder RW, Glasser DB: Antibiotic therapy for ocular infection. West J Med 1994; 161:579-584)

The appropriate use of antibiotics to treat ocular infection requires an understanding of the disease processes being treated and a knowledge of the pharmacology and pharmacokinetics of the drugs used. The prompt use of the appropriate antibiotics is essential to preserving vision in the presence of severe eye infection such as bacterial keratitis or endophthalmitis. We will review antibiotic therapy for various ocular infections. Commonly used antibiotics are shown in Table 1.*

General Principles of Antibiotic Therapy

Antibiotic therapy may result in killing the microorganism (bactericidal drugs) or inhibiting bacterial growth (bacteriostatic drugs). When bacteriostatic drugs are used to treat ocular infection, the host defense mechanisms are ultimately responsible for clearing and eradicating the infective organism. In bacterial keratitis, the infection develops in the avascular cornea, and in endophthalmitis it develops in the fluid-filled aqueous or vitreous cavity. In either case, the immune system may be unable to control the organism fast enough to prevent sight-threatening sequelae. Within the first 24 hours pathogens may multiply and release toxins and degradative enzymes that destroy the function and integrity of ocular tissues. Thus, bactericidal drugs are preferred for the treatment of severe ocular infection. The penicillins, cephalosporins, aminoglycosides, and fluoroquinolones are bactericidal agents and are generally used to treat ocular infection. Tetracycline, erythromycin, chloramphenicol, and sulfonamide are bacteriostatic and are often reserved for less severe infections or where there is a specific benefit such as tetracycline in the treatment of ocular rosacea.

Antimicrobial resistance is a constant concern to physicians, and resistance is found to ampicillin, gentamicin, tobramycin, newer cephalosporins, and fluoroquinolones.[1-4] In general, it is thought that with frequent and persistent long-term use of a given antibiotic, there is a greater chance of bacterial strains developing with resistance to that drug. To date, there have been no studies documenting increased resistance of bacteria following the treatment of acute bacterial conjunctivitis or following the short-term use of prophylactic topical antibiotics. It may be that increased antibiotic resistance for a given drug is related to the total area of the body treated or the systemic concentrations of the drug. Thus, antibiotics administered topically to the eye may not affect bacterial resistance to a substantial degree. On the other hand, there remains legitimate concern that drug resistance will occur when topical antibiotics (particularly bacteriostatic agents) are used for prolonged periods.

Topically applied antibiotics are capable of delivering high concentrations of antibiotics to the site of infection in most cases. With conjunctivitis and keratitis, the antibiotic is directly applied (by topical drops or ointments) to the area of infection. With endophthalmitis, topical antibiotics must transit the cornea, and therapeutic concentrations may not be achieved within the eye.[5,6] The factors that influence the intraocular penetration of antibiotics include the charge of the drug, the status of the corneal epithelium, the degree of ocular inflammation, the formulation and concentration of the drug, and the dosage regimen employed.[7] The chemical properties of a drug influence its intraocular penetration through its ability to diffuse across the layers of the cornea. The outer epithelial layer is rich in lipids, whereas the inner stroma of the cornea is composed primarily of water (about 70%). Biphasic solubility is necessary for a molecule to diffuse across both the epithelium and the stroma. The pH and buffering system of an antibiotic's formulation can profoundly influence its ocular penetration, as can the molecular size of the drug.[5,6] Most commonly used ophthalmic antibiotics are molecu-

*See also the editorial by J. P. Whitcher, MD, MPH, "Ocular Infections—A Rational Approach to Antibiotic Therapy," on pages 615-617 of this issue.

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TABLE 1.—*Antibiotics Commonly Used for Eye Infection*

Diagnosis	*Antibiotic*	*Dosage*
Bacterial conjunctivitis	Trimethoprim sulfate and polymyxin B sulfate (Polytrim)	q 1-2 hr while awake
	Ciprofloxacin HCl 0.3%	q 1-2 hr while awake
	Gentamicin sulfate or tobramycin 0.3%	q 1-2 hr while awake
	Sulfacetamide sodium 10%	q 1-2 hr while awake
Bacterial keratitis	Cefamandole nafate 5%	q ½-1 hr around the clock
	plus	
	Tobramycin 2%	
	or	
	Ciprofloxacin HCl 0.3%	q ½-1 hr around the clock
	Ofloxacin 0.3%	q ½-1 hr around the clock
Endophthalmitis		
Intravitreal	Vancomycin HCl	1 mg
	plus	
	Amikacin sulfate	0.4 mg
Subconjunctival	Vancomycin HCl	25 mg 2×/day
	Ceftazidime	100 mg 2×/day
Topical	Vancomycin HCl 5%	q ½-1 hr around the clock
	plus	
	Amikacin sulfate 2%	
Parenteral	Amikacin sulfate	Per manufacturer's recommendations
	plus	
	Ceftazidime	
Orbital cellulitis		
Children	Cefuroxime sodium	100 mg/kg/day in divided doses IV
Adults	Ceftizoxime sodium	2 grams q 8 hr IV

HCl = hydrochloride, IV = intravenous, q = every

larly small enough to diffuse through biologic membranes without difficulty, but bacitracin and colistin and other polymyxins are higher-molecular-weight antibiotics that penetrate the cornea poorly.[5]

Some drug formulations can cause microdisruption of the corneal epithelium, and this "microtoxicity" enhances drug penetration because the epithelium is the principal barrier to drug penetration. This is thought to occur when ethylenediaminetetra-acetate (EDTA) or sodium benzoate are used as preservatives. Ocular inflammation may also result in damage to the corneal epithelial barrier and enhance penetration.[5-7] The turnover of the tear film is relatively rapid, and formulations that increase the persistence of the drug in the tear film may enhance drug concentrations. This can be accomplished by making the preparation more viscous or by placing it in an ointment form. In theory, ointments have superior bioavailability to solutions because of the increased contact time on the eye. Hydrophilic antibiotics, however, may crystallize within the ointment base, which then prevents their release and subsequent penetration, with the net effect of decreasing their bioavailability.

Increasing the concentration of the antibiotic will increase the diffusion gradient across the cornea and enhance its penetration.[5,8] The formulation of topical antibiotics in "fortified" strengths may be limited by the solubility or toxicity of an individual antibiotic. Fortified preparations produce substantially higher drug concentrations in the cornea and aqueous humor and are more effective in killing microorganisms in experimental models of bacterial keratitis than are standard-strength solutions.[9-12] Fortified antibiotics are therefore frequently used to treat bacterial keratitis. The newer fluoroquinolones are an exception and have not been formulated in fortified antibiotic preparations. Ciprofloxacin in the commercially available concentration of 0.3% (3 mg per ml) has been shown to yield therapeutic corneal levels, and more recently, ofloxacin has been shown to produce both therapeutic cornea and aqueous levels when a commercial-strength 0.3% solution is used for dosing.[13,14]

Specific dosing techniques can also be used to advantage in topical therapy for serious ocular infection. A loading regimen of one drop every minute for 5 minutes, repeated 60 minutes later, is capable of producing high concentrations of antibiotic within the cornea (well above 100 μg per gram of tissue).[15] The sustained administration of an antibiotic—one drop of 0.3% gentamicin sulfate every 30 to 60 minutes—appears optimal.[16,17] When more than one antibiotic is used, five minutes should elapse between installations to prevent a "washout" of the first antibiotic.

Toxicity of topically applied antimicrobials may be related to the antibiotic or to the preservatives and vehicles

used in the formulation. Antibiotics may retard epithelial healing, and this may occur to a greater extent with fortified solutions.[17,18] Thimerosal, a mercurial compound with relatively weak antimicrobial activity, can cause hypersensitivity reactions, keratoconjunctivitis with coarse corneal epithelial changes, giant papillary conjunctivitis, corneal stromal infiltrates, and calcific band keratopathy.[19-23]

Benzalkonium chloride is known to inhibit epithelial adhesion, cause a loss of superficial epithelial cells, and delay healing of the epithelium. These epithelial toxic effects and the surfactant properties of benzalkonium may enhance the penetration of topically applied antibiotics.[24,25]

The administration of antibiotics into the vitreous cavity is advocated for the treatment of endophthalmitis. This disease has a poor prognosis despite aggressive treatment with topical, parenteral, and periocular antibiotics.[26] Conventional routes of antibiotic administration (topical and parenteral) are unable to produce sustained therapeutic antibiotic concentrations in the vitreous, thereby mandating direct intravitreal administration whereby therapeutic antibiotic levels may be maintained for relatively long periods of time (gentamicin has a half-life of 33 hours in the primate vitreous).[27] Retinal toxicity of antibiotics administered to the vitreous cavity is the main problem with intraocular therapy. In animal and clinical trials in humans, it is thought that the maximum tolerable doses are 100 to 400 μg for gentamicin, 2 mg for cefazolin or methicillin, 400 μg for amikacin, and 1 mg for vancomycin.[26-31] Because of the narrow range between the therapeutic dose and toxicity of the aminoglycosides, it is essential that the medications are carefully and properly prepared and that injections are made into the anterior or mid-vitreous to avoid excessively high concentrations near the retina.

Parenteral antibiotics are indicated in patients with preseptal cellulitis, orbital cellulitis, dacryocystitis, and as an adjunct in the treatment of endophthalmitis or keratitis with scleral extension or impending or actual corneal perforation. In addition, corneal or conjunctival infections with *Neisseria gonorrhoeae* at any age or *Pseudomonas*, *Haemophilus*, and *Chlamydia* species in neonates should be treated with parenteral antibiotics.

Topical antibiotics are effective and safe when used as prophylaxis against endophthalmitis after surgical therapy and to decrease the risk following penetrating trauma.[32-37] Antibiotics may best be administered at least 24 hours before an operation to effectively minimize the bacterial counts in the conjunctival cul-de-sac.[38] The subconjunctival administration of antibiotic following an intraocular operation has been shown effective in animal models and is commonly used.[39,40] On rare occasions, severe retinal toxic reactions have occurred with the postoperative administration of subconjunctival aminoglycoside, and cephalosporin administration may be preferred. Most of these reactions have been associated with inadvertent scleral perforation during the drug administration.[41] Visualization of the needle tip during administration will reduce this risk.

Severe ocular infections such as bacterial keratitis, endophthalmitis, or orbital cellulitis are clear indications for aggressive antibiotic therapy with broad-spectrum drugs. In most cases, the initial choice of antibiotic must be made without knowing the identity or susceptibility of the infecting organism. In bacterial keratitis and endophthalmitis, specimens from the infected site should be obtained for culture and smear before the antimicrobial therapy is administered, and this should be done promptly so as to avoid any delay in treatment.[42]

Bacterial Keratitis

Bacterial keratitis refers to bacterial infection of the cornea. The surface epithelium, the mechanical properties of the lids, and bioactive components of the tear film provide an effective barrier to infection. Infection may occur when these barriers are compromised and may then lead rapidly to ulceration of the cornea with resultant surface irregularity or corneal scarring, with associated loss in visual function. The early treatment of bacterial keratitis with adequate doses of the appropriate antibiotic is essential to minimize the loss of vision.

Because the invading organism is usually not immediately known, broad-spectrum antibiotics are chosen as the initial therapy for severe infections so that all possible gram-positive and gram-negative pathogens are covered. In the treatment of bacterial keratitis, this typical "shotgun" approach to treatment is begun with a combination of cephalosporin and aminoglycoside. The antibiotics are also formulated in fortified concentrations to provide the highest possible concentrations of antibiotic before toxicity is attained, so that bactericidal levels can be quickly established in the cornea. In a typical regimen, 2% tobramycin and 5% cefamandole nafate may be used. After a loading regimen, the antibiotic administration is continued every half hour around the clock for the first 24 hours, with a gradual tapering of this dosage over the ensuing days as therapeutic effect is observed. Once the results of cultures and antibiotic sensitivity patterns are reported, the therapy can be modified to single-drug coverage as indicated.

A second alternative is to use the newer fluoroquinolones as single-drug coverage for bacterial keratitis. This single-drug regimen is probably much easier for the patient or care giver to administer and thus has the theoretical advantage of enhanced compliance. There has been some controversy over the single use of the fluoroquinolones because of concern that perhaps some of the organisms, such as *Streptococcus pneumoniae*, may not be covered adequately. With the corneal drug concentrations that are obtainable with topical ciprofloxacin therapy (3.1 μg per gram of tissue), this may not be a legitimate concern.[43] Ciprofloxacin hydrochloride in a 0.3% solution as a single agent and given every hour has been shown to be efficacious in a prospective multicenter study of the treatment of bacterial keratitis.[44] More recently, ofloxacin has been formulated for topical ocular antibiotic therapy and may also prove efficacious because higher aqueous levels of ofloxacin can be attained with comparative dosing regimens.[14]

Subconjunctival and intravenous antibiotics are traditionally reserved for cases of impending ocular perforation or when the infectious process appears to extend into

TABLE 2.—*Initial Therapy for Endophthalmitis*

Route of Administration	Traumatic Infection	Postoperative Infection Protocols: Endophthalmitis Vitrectomy Study*	Postoperative Infection Protocols: Bascom Palmer Eye Institute†
Intravitreal (in 0.1 ml)	Vancomycin HCl, 1 mg Amikacin sulfate, 0.4 mg‡	Vancomycin HCl, 1 mg Amikacin sulfate, 0.4 mg	Vancomycin HCl, 1 mg Ceftazidime, 2.25 mg Dexamethasone, 0.4 mg
Subconjunctival (in 0.5 ml)	Vancomycin HCl, 25 mg Gentamicin sulfate, 20 mg	Vancomycin HCl, 25 mg Ceftazidime, 100 mg	Vancomycin HCl, 25 mg Ceftazidime, 25-50 mg Dexamethasone, 12-24 mg
Topical	Vancomycin HCl, 5% Gentamicin sulfate, 0.14%	Vancomycin HCl, 5% Amikacin sulfate	Vancomycin HCl, 5% Ceftazidime, 5% Corticosteroids
Parenteral	Clindamycin phosphate Amikacin sulfate Ciprofloxacin HCl	Amikacin sulfate Ceftazidime	Vancomycin HCl Ceftazidime

HCl = hydrochloride

*From the National Eye Institute ("Manual of Operations," Data Coordinating Center, University of Pittsburgh, Pittsburgh, Pennsylvania, 1990).
†From H. W. Flynn, MD, and T. G. Murray, MD, Bascom Palmer Eye Institute, Miami, Florida, written communication, November 1994.
‡For *Bacillus* species, add clindamycin phosphate, 0.25 mg.

the sclera. Administering drugs subconjunctivally is painful and causes scarring of the conjunctiva. The concentration of antibiotic obtained is greater than can be obtained with frequent topical dosing, but the concentrations are not typically maintained beyond a few hours.[45]

There has been recent interest in using collagen shields (contact lenses fashioned out of animal collagen) soaked in various antibiotics. When placed in the eye, they may result in high corneal or aqueous levels of antibiotic; however, they prevent the cleansing or toileting action of the lids and tear film and may sequester bacterial toxins and enzymes at the site of a corneal or scleral infection.

Endophthalmitis

Endophthalmitis or infection within the eye is potentially the most devastating of ocular infections and a vision-threatening ocular emergency that mandates immediate and aggressive antibiotic therapy. Endophthalmitis occurs most frequently following penetrating trauma, but may also occur after an intraocular operation. Rare cases occur by spread from the bloodstream. Any pathogenic organism can cause endophthalmitis following a penetrating injury. Bacilli are seen more frequently than in nontraumatic endophthalmitis. The organisms most commonly associated with endophthalmitis after surgical therapy are the same as those that colonize the lids, namely, *Staphylococcus aureus*, *S epidermidis*, several *Streptococcus* species, and assorted gram-negative rods. The bacteria themselves may release toxins and enzymes that destroy the retina, and the host inflammation can also compromise delicate intraocular structures. Antibiotic therapy for endophthalmitis is most effective in preserving visual function if initiated during the first few hours following early clinical detection and before there is substantial tissue destruction. The eye is first cultured with specimens taken from the conjunctival cul-de-sac, and then intravitreal aspirates are obtained either with a cutting vitrectomy instrument or by a 23-gauge needle passed through the sclera at the pars plana. Intravitreal antibiotics are then administered. Subconjunctival antibiotics, fortified drops, and intravenous therapy are begun. The antibiotics chosen should provide an initial broad spectrum. The antibiotics and their dosages are given in Table 2.

Conjunctivitis

Conjunctivitis is often synonymous with red eye and is simply an inflammation of the conjunctiva. It may be caused by allergic or toxic stimuli, bacteria, or viruses. Allergic conjunctivitis is typically seasonal, with the main symptom of itching, and may present with a ropy mucin-like discharge or minimal discharge and an inflamed conjunctiva. Viral conjunctivitis usually affects first one eye and then, in about a third of the cases, the fellow eye. Patients have irritation and possible photophobia and present with a clear watery discharge, preauricular lymphadenopathy, and occasionally an associated pharyngitis. The hallmark of bacterial conjunctivitis is ocular irritation, inflamed conjunctivae, and a purulent discharge. The most common organisms identified in adult patients with bacterial conjunctivitis are *S aureus*; *S epidermidis*; *Streptococcus*, *Haemophilus*, *Acinetobacter*, and *Corynebacterium* species; *S pneumoniae*; and *Proteus* or *Morganella morganii*.[46] Because bacterial conjunctivitis is common and infection is generally not severe, physicians often do not consider it a serious disease and specimens are not taken for culture; rather, empiric topical antibiotic therapy is started. Broad-spectrum antibiotics such as the combination of trimethoprim sulfate and polymyxin B sulfate (Polytrim, Allergan Pharmaceutical Corporation) provide coverage against both gram-positive and gram-negative organisms, are well tol-

erated on the eye, and may be an excellent choice for the treatment of conjunctivitis.[47] Ciprofloxacin hydrochloride (Ciloxan, Alcon Laboratories, Inc) has also been shown to be effective in treating bacterial conjunctivitis.[48] The aminoglycosides gentamicin sulfate and tobramycin have also been widely used with good results. Sulfacetamide sodium in a 10% solution is also commonly used to treat bacterial conjunctivitis, but produces some stinging, particularly in younger patients.[49]

In conjunctivitis in children, the bacterial organisms identified are somewhat different from those seen in adults. In a study by Gigliotti and co-workers, *H influenzae* and *S pneumoniae* were found to be the most common bacteria isolated rather than the *Staphylococcus* species.[50] Polytrim again seems to be a reasonable choice because of the coverage of both the *Streptococcus* and *Haemophilus* species.

Some patients will have a hyperacute conjunctivitis with prominent chemosis and purulent discharge from the eye. Cultures and Gram's stain should be done because *N gonorrhoeae* may be identified. If the gonococcus is identified, then these patients should also be treated with parenteral antibiotics.

Orbital Cellulitis

Orbital and periorbital infections may be caused by a variety of organisms including bacteria, fungi, and parasites. Infection may be initiated from both surgical and nonsurgical trauma or by a retained foreign body. An infecting organism may also extend into the orbit or periorbital tissue from the conjunctiva, the globe itself, the lacrimal sac, or from the paranasal sinuses. Less frequently, orbital involvement may follow hematogenous spread from other sites in the body. Ophthalmologists generally separate orbital and periorbital infection into subgroups that include preseptal cellulitis, orbital cellulitis, and subperiosteal or intraorbital abscess. Cavernous sinus thrombosis occurs less frequently. Preseptal (outside the orbital septum) cellulitis requires parenteral antibiotic therapy, and the drug of choice will depend on the postulated overlying cause of the disease. Orbital involvement mandates not only parenteral antibiotic therapy but also consideration of the surgical drainage of an infectious focus. This is particularly the case for a subperiosteal abscess where the growing abscess is within the closed space of the orbital mass and may cause increased pressure on the globe, compromising blood flow to the eye. A more thorough description of the medical and surgical management of infections of the orbit is presented by Gonnering and Harris.[51]

Dacryocystitis

Infections of the lacrimal sac are common. They may occur at any age and are usually the result of either an acquired or congenital obstruction of the nasolacrimal duct. Definitive treatment depends on reestablishing a patent drainage system. Acute dacryocystitis with signs of overlying inflammation and cellulitis should initially be treated with parenteral antibiotics—1 gram of oral dicloxacillin sodium per day in divided doses for 10 to 14 days—and topical antibiotics until the infection is controlled. Antibiotic therapy can be changed based on the patient's response and results of culture and sensitivity tests. Before antibiotic treatment, any discharge material should be cultured. Hot compresses to the skin overlying the inflamed lacrimal sac may assist in drainage, and the ophthalmologist may also attempt to drain the swollen sac with nasolacrimal probing or external fistulization if the sac is excessively swollen and tender. Once the acute infection is controlled, the antibiotic doses are tapered and the patient's condition reevaluated. Persistent obstruction of the nasolacrimal duct usually requires surgical intervention to prevent recurrent infection or persistent epiphora.

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Increased Erythrocyte Sedimentation Rate and a Splenic Mass
Clinicopathologic Conference

Discussants
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This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it has been edited by Jonathan G. Drachman, MD, Chief Medical Resident; Henry Rosen, MD, Professor and Associate Chair; and Paul G. Ramsey, MD, Professor and Chair of the Department of Medicine.

Case Presentation

JONATHAN G. DRACHMAN, MD*: A 34-year-old man was referred to the infectious diseases clinic at the University of Washington Medical Center for a second opinion and evaluation of a splenic mass associated with an increased erythrocyte sedimentation rate (ESR).

In 1987 the patient was found to have an ESR of 85 mm per hour during routine physical examination and laboratory evaluation for insurance screening. Repeated studies confirmed the abnormal result (ESR range, 60 to 105 mm per hour). The patient remained asymptomatic, and no abnormalities were detected on the physical examination. Additional workup revealed moderate anemia (hematocrit, 0.32 [32%]) with hypochromic, microcytic erythrocytes. A bone marrow biopsy revealed normal iron stores, consistent with anemia of chronic disease.

No further evaluation was done until the patient established care with a local internist in May 1992. At that time, the patient admitted to having occasional headaches and fatigue, but otherwise claimed to be in good health. He did not have fevers, night sweats, rash, arthralgias, myalgias, lymphadenopathy, or abdominal pain. He was not taking any medications. There was no history of recreational drug use. He was a nonsmoker and drank alcohol only rarely. He was born in Boise, Idaho, and moved to Seattle in his early 20s. His job as an international businessman required extensive foreign travel to Europe (France, Italy, Spain), South America (Argentina, Ecuador, Peru, Chile), and Asia (Hong Kong, Japan, China, Thailand). He was married and lived with his wife and two cats in the Seattle area.

An enlarged spleen was then palpable in the left upper quadrant of the abdomen; the physical examination otherwise showed no abnormalities. An extensive workup followed. A tuberculin skin test using intermediate-strength purified-protein derivative was negative (with positive controls). Hematologic studies showed a hematocrit of 0.36 (36%), a leukocyte count of 8×10^9 per liter (8,000 per mm^3) with a normal differential (no eosinophilia), an ESR of 95 mm per hour, and a fibrinogen level of 720 ng per dl. Serum electrolyte, creatinine, and liver function test values were unremarkable. Blood cultures were negative. Bone marrow aspiration and biopsy were done, revealing no bacterial, fungal, or mycobacterial organisms using appropriate stains and cultures; there was no evidence of neoplasia in the marrow. Tests for antinuclear antibodies and rheumatoid factor were normal. Serum protein electrophoresis showed hypergammaglobulinemia without a spike (consistent with inflammation). Assays for cryoglobulins and cryofibrinogens were negative.

A chest radiograph showed a slightly elevated left hemidiaphragm and no lung infiltrates, nodules, or mediastinal adenopathy. An abdominal computed tomographic (CT) scan (Figure 1) demonstrated a large splenic mass ($9 \times 8 \times 9$ cm) with scattered calcifications and two small (1 to 2 cm) noncalcified hypodense lesions. The liver and kidneys were normal, and no abdominal adenopathy was identified.

The patient was referred to an infectious disease consultant, who considered the diagnosis of schistosomiasis, given the splenic mass and travel history. Tests of stool and urine specimens were negative for ova and parasites. An intravenous pyelogram was normal, and rectal biopsy results also did not show schistosomiasis.

The splenic masses, increased ESR, and anemia of chronic disease remained a mystery. A splenectomy was recommended for diagnosis and possible therapy. The pa-

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ABBREVIATIONS USED IN TEXT
CT = computed tomographic
ESR = erythrocyte sedimentation rate

tient was referred to this institution for a second opinion as to the cause of the illness and the necessity for this operation.

Discussion

JAN V. HIRSCHMANN, MD*: The patient's travel history looms as an important element to consider in trying to uncover the correct diagnosis. The other salient points include an increased ESR and anemia of chronic disease, both present for at least five years; splenic masses with evidence on CT scan of scattered calcifications, but without contents of water density to suggest cystic structures; and an absence of symptoms.

An impulse to cut away what seems inessential is known as Ockham's (or Occam's) razor, named after a 14th-century English religious philosopher, William of Ockham. Also called the law of parsimony, this concept states that entities should not be multiplied needlessly, or in other words, that the simplest of competing theories is preferable. The "razor" excises unnecessary information or concepts. Accordingly, I will assume that the splenic masses and the long-standing laboratory abnormalities are related. Ockham's razor, however, has limitations. Discerning what is superfluous, for example, may be difficult. Furthermore, although the law of parsimony is usually reasonable in young, otherwise healthy persons, when people age, become chronically ill, or have immunodeficiency, several diseases often coexist, and attempting to explain all clinical findings by a single disorder may be misleading. A recent editorial reflects this problem in its title, "Is Occam's razor disposable?"[1] Nevertheless, in considering the young, robust patient in the present case, I will employ this sharp instrument.

What information does a review of the patient's long-standing anemia and an elevated ESR provide? The anemia of chronic disease,[2] once called "chronic, simple anemia," has several aliases, including "anemia of chronic disorders"[3] and "anemia of inflammation,"[4] proposed because inflammation seems present in most, perhaps all, of the underlying conditions. The important features of this disorder include a decrease in both serum iron levels and total iron-binding capacity, with the saturation typically 10% to 20%, compared with the normal of about 20% to 45%. In about a fifth of patients with anemia of chronic disease, however, the saturation is below 10%—a level that creates confusion with iron-deficiency anemia—but the serum ferritin level, which is low in iron deficiency, is normal or elevated. Furthermore, iron is present in bone marrow aspirates, which also reveal that the iron-containing nucleated erythrocytes (sideroblasts) constitute less than 30% of the total number of nucleated erythrocytes, compared with the normal of 30% to 50%. The decreased number of iron granules in the erythrocyte precursors despite the abundant amount of marrow iron suggests that the major pathogenic factor is the imprisonment of iron in the marrow. As is so often the case, such a simple explanation is misleading, and the problem, instead, is diminished production caused by the actions of cytokines.[5] Interleukin-1, tumor necrosis factor, and interferon alfa, produced during inflammation, inhibit erythroid precursors, decrease erythropoietin production, and impair iron release. High-dose erythropoietin, however, can overcome these effects and correct the anemia.[5]

Anemia of chronic disease is commonly normochromic and normocytic. In about 50% of patients, however, the mean corpuscular hemoglobin concentration is low, indicating hypochromia, and in 20% to 30% the mean corpuscular volume is reduced, signifying microcytosis.[6,7] The hematocrit usually becomes stable at a level above 0.30 after about two months, but in 20% it is less than 0.25. A review of the records of patients admitted to a hospital with this type of anemia found that 35% had acute or chronic infections, 20% had malignant neoplasms, 15% had renal insufficiency, and 5% had rheumatic diseases.[7] Miscellaneous problems constituted the remaining 25%; among these were several with chronic noninflammatory disorders, such as congestive heart failure and obstructive lung disease, infirmities not traditionally associated with this type of anemia.

The increased ESR in this case is another nonspecific finding. Originally developed in 1918 as a test for pregnancy, the ESR measures the distance in millimeters that erythrocytes fall in a glass tube in one hour.[8,9] Being negatively charged, erythrocytes repel each other and settle slowly. Certain plasma proteins, especially fibrinogen but also the globulins, are positively charged, promote

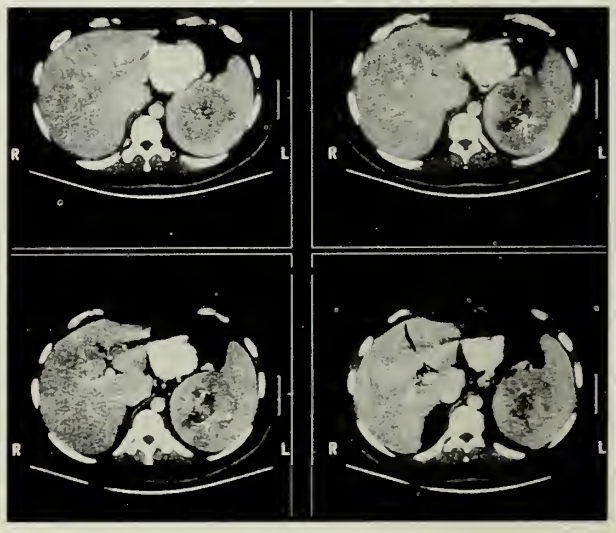

Figure 1.—The abdominal computed tomograms of sequential cuts through the abdomen demonstrate a single, large hypodense mass in the spleen with scattered calcification. The stomach is partially opacified by an oral contrast medium; the liver and kidneys appear normal, and no abdominal adenopathy is visible.

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erythrocyte aggregation (or rouleaux formation), and increase the ESR above the normal rate of about 20 mm per hour. In a large group of outpatients, when the ESR was between 75 and 99 mm per hour, which occurred in about 4%, the underlying disorders were infection in 15%; renal disease, rheumatic disorders, and malignant lesions in 10% each; and miscellaneous illnesses in 5%; the cause was unknown in 50%.[10] Once the rate exceeds 100 mm per hour, however, a diagnosis is nearly always evident: infection, usually acute, in about 35%; cancer, usually metastatic, in 25%; rheumatic disorders in 15%; renal disease in 5%; miscellaneous conditions in 15%; and unknown in only about 5%.[10-15] A markedly increased ESR, like anemia of chronic disease, is compatible with many disorders, but most strongly implies an infectious or malignant cause, a conclusion that does not substantially advance the primary diagnostic considerations of splenic masses. Yet these laboratory findings are, curiously, a crux in this case, for they indicate that the patient has probably had his splenic process for at least five years, an important point in exploring the possible diagnoses.

Among possible infections, the most arresting feature in this patient is his extensive travel history, suggesting especially a parasitic disorder—several of which commonly cause splenomegaly—including malaria, schistosomiasis, toxoplasmosis, and leishmaniasis (kala-azar). These disorders produce enlarged spleens, sometimes to gargantuan proportions, but the pathologic findings are granulomas—as an inflammatory response to the microorganisms—not masses.[16] An additional mechanism in schistosomiasis is liver infestation causing portal hypertension and, consequently, congestive splenomegaly.[17] Echinococcal infection, however, can cause splenic masses, usually associated with similar masses in the liver, but these are cysts with contents of water density, not the findings on CT in this patient.

Four types of chronic bacterial infections merit brief scrutiny. Brucellosis develops from ingesting organisms originating in cattle, sheep, goats, swine, and dogs; in some patients splenic abscesses may be present for years,[18] but they produce symptoms, such as fever and weight loss, at least intermittently. *Mycobacterium tuberculosis* can infect the spleen, but the lack of organ involvement elsewhere in this patient, especially in the lungs, is unusual, and the negative tuberculin test despite intact cutaneous hypersensitivity to other antigens nearly exonerates the presence of active infection,[19] although it does not completely exclude it. Tertiary syphilis can result in a splenic gumma, a mass of granulomatous inflammation, but this is a rare manifestation of *Treponema pallidum* infection.[20] Melioidosis, an infection with *Pseudomonas pseudomallei*, a gram-negative bacillus found in Asia, can be acute or chronic and, like tuberculosis, may be latent for years. Although infection of the spleen occurs, most patients have a history of a preceding febrile disease, usually with lung involvement, and roentgenographic evidence of a current pulmonary inflammatory process.[21]

In theory, an untreated splenic abscess could partially resorb, leaving a mass with calcifications, but several factors militate against such a diagnosis. Patients with splenic abscesses, about 30% of whom are immunocompromised, typically have an obvious predisposing factor, most commonly (about 55% of cases) an infection causing bacteremia, such as endocarditis or urinary tract sepsis. In about 20% the underlying process is trauma and in 10% hemolytic anemia, wherein splenic congestion with destroyed erythrocytes causes ischemia or hemorrhage. In both these settings, a transient, asymptomatic bacteremia presumably infects hematomas, necrotic tissue, or ischemic foci, against which local defense mechanisms are ineffective. In 5% of cases of splenic abscess, the infection spreads from a contiguous, usually intra-abdominal, area of suppuration. In only 10% of cases is no predisposing factor evident.[22,23] The responsible organisms, such as *Staphylococcus aureus*, streptococci, and *Salmonella* and *Candida* species, are typically aggressive, and, not surprising, most patients are acutely ill, with symptoms present for one to three weeks. About 90% are febrile, 60% have generalized or left upper quadrant abdominal pain, and 90% have leukocytosis. The absence of these characteristics in this patient makes splenic abscess unlikely.

With no infectious cause providing a credible diagnosis, neoplasms should be considered. Splenic metastases are detectable in about 2% to 9% of cancers at autopsy,[24] the most frequent primary sites being the lungs, breasts, and skin (malignant melanoma). In a nonsmoker with a normal chest film, an occult bronchogenic carcinoma is highly improbable. Breast cancers can develop in men, but only 6% occur in patients younger than 40, the primary cancer is usually obvious on physical examination, and this cancer, in men as in women, rarely presents as a metastatic cancer of unknown primary.[25] Malignant melanomas deserve careful consideration, however. With this protean tumor, the interval between the discovery of the primary and the subsequent appearance of a metastasis is sometimes decades.[26] It is conceivable that the patient previously had a skin lesion not recognized as a melanoma that was removed or destroyed by cautery, cryosurgery, or other trauma. An alternative scenario is that the primary tumor disappeared on its own. In an extensive review of the spontaneous regression of cancer, malignant melanoma accounted for 11% of the reported cases, the third most frequent cause behind renal cell carcinoma and neuroblastoma in children.[27] Nevertheless, splenic metastases, even in patients with malignant melanoma, usually occur with obvious, widespread disease elsewhere.

Primary benign tumors of the spleen include hamartoma, hemangioma, or lymphangioma.[28] None are likely to have the CT appearance seen in this patient or to cause the anemia of chronic disease and an increased ESR. Primary splenic cancers, which are rare, apparently arise from vascular endothelium. Although some authorities have separated angiosarcomas from hemangioendotheliomas,[29] others label all such vascular tumors angiosarcomas.[16,30,31] These neoplasms are usually not just malignant, but virulent. They are nearly always aggressive, often

spreading locally or metastasizing early to lymph nodes, lung, or liver. Few patients survive more than a year. Another splenic neoplasm, malignant fibrous histiocytoma, also displays virulence.[30] These clinical features make primary splenic cancer an unlikely candidate for an asymptomatic disease that has been present for at least five years.

Another consideration is a malignant lymphoreticular disorder. Primary splenic Hodgkin's disease is rare, but disease confined to the spleen occurs in about 1% to 2% of patients with non-Hodgkin's lymphoma.[32-34] The gross pathologic appearance may be homogeneous enlargement, miliary nodules 1 to 5 mm in diameter, or masses greater than 2 cm in diameter. Because non-Hodgkin's lymphoma can cause anemia of chronic disease and an increased ESR, produce no symptoms, and produce masses in the spleen, even with areas of calcification,[35] this diagnosis is plausible. With non-Hodgkin's lymphomas, however, the kinds that can be asymptomatic do not cause splenic masses, and the type that causes masses (large-cell lymphoma) is an aggressive, symptomatic cancer highly unlikely to be latent for five years.[36]

I have surveyed the possibilities of both infections and neoplasms and found no plausible diagnosis. Is there another way to bring together tumors and inflammation? Several inflammatory disorders have features like neoplasms; two that can involve the spleen are giant lymph node hyperplasia (Castleman's disease) and inflammatory pseudotumor. Castleman's disease typically causes obvious lymph node enlargement, especially in the mediastinum. Although multicentric disease can result in splenic masses, the absence of lymphadenopathy on physical examination, chest radiograph, and abdominal CT scan makes this diagnosis unlikely.[37] Inflammatory pseudotumors are masses of unknown cause characterized by nonspecific inflammation consisting of lymphocytes, plasma cells, histiocytes, and fibrosis in varying combinations.[38] Although described more frequently in the lungs and orbits, in 15 reported cases the spleen was involved. The patients, whose ages ranged from 19 to 75, had various presentations, including fever, anemia, and splenomegaly; some had no symptoms. In one patient splenic calcification was apparent on the CT scan.[39] Inflammatory pseudotumors are single or multiple, sharply demarcated or poorly circumscribed masses, often of impressive dimensions (as much as 12.7 cm in diameter). This disorder could explain all the elements in this case, including the lack of symptoms, the lengthy duration, the laboratory abnormalities, and the CT findings. I therefore declare that the diagnosis is inflammatory pseudotumor of the spleen.

Before concluding, however, I shall address the question of splenectomy. This procedure has important complications, both in the perioperative period and afterwards. The risks of immediate problems seem related, in part, to the reason for the operation and the age of the patient, with complications occurring more frequently in older patients.[40] When performed for trauma or incidentally during a surgical procedure for another purpose, such as gastrectomy, the morbidity is about 30% and the mortality 15%. When the reason is an underlying hematologic disease, such as hemolytic anemia, immune thrombocytopenia, or leukemia, splenectomy incurs a morbidity of about 25% and a mortality of 10%.[41-43] Perhaps the most analogous situation to that of our patient is splenic removal during staging laparotomy for Hodgkin's disease, a disorder primarily of the young, in which the morbidity is about 10% and the mortality 5%. The complications are primarily respiratory and infectious, but thromboembolic phenomena, including leg vein thrombi, pulmonary emboli, and mesenteric venous occlusion occur in about 1% to 2% of patients, presumably related to the thrombocytosis that develops following splenectomy.

Splenic removal also imposes long-term risks. In addition to its main function of weeding out the weak, misshapen, and aged erythrocytes, the spleen removes particulate matter, including microorganisms, from the circulation. It also produces immunoglobulin M and cytokines in response to acute infections and synthesizes components of the alternative pathway of complement activation. The absence of these filtering and immunologic functions predisposes asplenic patients to an apparent increase in the frequency and severity of certain infectious diseases. Those caused by intraerythrocytic parasites like malaria seem more virulent. The best information exists for *Babesia microti*,[44] an organism that infects erythrocytes and is transmitted to humans by the same tick, *Ixodes dammini*, that transmits Lyme disease. This parasite also lives in the species of mice that *Borrelia burgdorferi* infects. Babesiosis occurs primarily in certain coastal areas of the Northeast, where it can cause inapparent infections. Symptomatic disease may be more frequent in patients without spleens in whom fever, myalgias, hemolytic anemia, and renal failure have occurred. Because this organism is difficult to treat and may be lethal, asplenic patients should probably avoid certain areas of the Northeast. Indeed, avoiding these areas of the Northeast is prudent for people *with* spleens.

Another infectious agent seemingly more virulent in asplenic hosts is a gram-negative bacillus recently named *Capnocytophaga canimorsus* (previously designated DF-2).[45] A part of the normal mouth flora of dogs, it can cause severe infection following dog bites; in patients without spleens, bacteremia with disseminated intravascular coagulation and peripheral gangrene has developed. Occasionally the disease has followed exposure to cats, making these two domestic beasts possibly dangerous for asplenic humans.

Although some authors express concern about *Neisseria meningitidis* (meningococcus) and *Haemophilus influenzae*, infections from these organisms may not be more frequent or severe in asplenic hosts. Clearly the most serious consideration is *Streptococcus pneumoniae*. Fatal pneumococcal sepsis following splenectomy occurs in children with a frequency of about 1 case per 300 patient-years.[46] If this rate were sustained during the adult years, the risk of this infection would obviously be substantial over the lifetime of someone undergoing splenec-

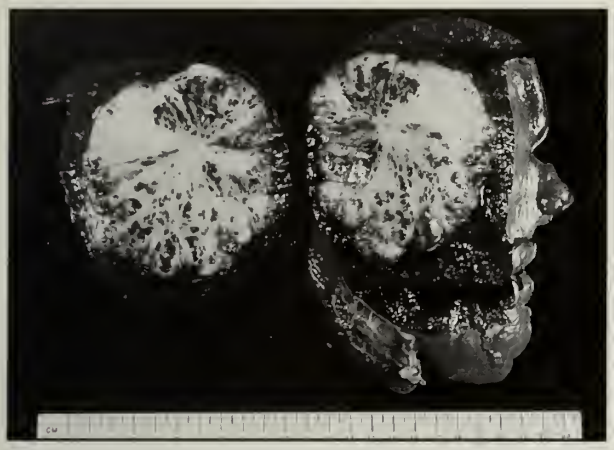

Figure 2.—The gross specimen of spleen, weighing 882 grams, contains a single expansile nodule 10 cm in diameter. Islands of dark (red) soft tissue are seen in a white, firm, fibrous-appearing stroma.

tomy during childhood. The incidence of fatal pneumococcal sepsis in adults is less, perhaps about 1 case per 1,000 patient-years. The risk is greater if the splenectomy was for malignant or hematologic disease rather than for trauma and is highest in the first few years after the procedure, although cases have occurred decades later. Primary bacteremia, sometimes complicated by meningitis, is the usual presentation, rather than a focal infection of the respiratory tract. Certain features occur in pneumococcal sepsis affecting asplenic hosts that are rarely, if ever, present in patients with spleens. These include disseminated intravascular coagulation, peripheral gangrene, hypoglycemia, and adrenal hemorrhage. The intensity of bacteremia is so great that organisms are sometimes visible on peripheral blood smears, indicating a concentration of about 10^6 bacteria per ml, compared with a level that rarely exceeds 200 bacteria per ml in patients with bacteremic pneumococcal pneumonia.[47] The mortality is about 60% to 70%, compared with about 20% in patients with bacteremic pneumococcal pneumonia. Patients with this disorder usually have nonspecific symptoms, such as fever, chills, sore throat, diarrhea, and myalgias, strongly suggesting a viral cause. Because pneumococcal sepsis is so frequently and rapidly fatal in asplenic hosts, clinicians should strongly suspect this possibility in those with an acute febrile disease, quickly obtain appropriate cultures, and institute antimicrobial therapy. Some authorities have recommended that asplenic patients have a supply of oral antibiotics to take immediately on having a febrile illness and then seek prompt medical attention. Some have also suggested regular penicillin prophylaxis, at least for the first few years after splenectomy in children, and preoperative administration of the pneumococcal vaccine, although its efficacy in these patients is unknown.

Splenectomy, therefore, imposes genuine immediate and long-term risks. In this patient, however, the clinical information does not allow a confident diagnosis of his underlying disease. This uncertainty, the possibility of a splenic malignant tumor, and the theoretical concern that an inflammatory pseudotumor, if present, could be premalignant support the plan for a diagnostic, and possibly therapeutic, splenectomy. Being a young and otherwise healthy adult, he has low risks for immediate postoperative complications, which are more common in older patients, and for later fulminant infections, which are much more frequent in children.

Clinical Diagnosis

Inflammatory pseudotumor of the spleen.

HENRY ROSEN, MD*: What was the opinion of the infectious disease consultants?

W. CONRAD LILES, MD, PhD†: Although parasitic diseases were still possible, we felt that this was most likely a benign tumor, probably of endothelial origin. We agreed with the recommendation for splenectomy and preoperative pneumococcal vaccination.

DR DRACHMAN: The patient underwent laparotomy and splenectomy at the Virginia Mason Hospital in Seattle. The pathologic evaluation will be presented by Susan Patterson, MD.

Pathology

SUSAN PATTERSON, MD‡: The spleen was 882 grams, 18 × 12 × 9 cm, and smoothly encapsulated. It contained a single 10-cm-in-diameter expansile nodule (Figure 2). On the cut surface, the nodule was variegated, tan to red, rubbery, and partially calcified, with an ill-defined, irregular, nonencapsulated border pushing against uninvolved spleen.

On histologic examination, the tumor consisted of "granulomatous-appearing," poorly defined nodules of endothelial cells forming slit-like vascular spaces. Endothelial cells varied from plump and epithelioid to spindle-shaped. Intracytoplasmic lumens could be identified. Cells displayed no anaplasia or notable numbers of mitoses. Endothelial cells were strongly positive for factor VIII by immunoperoxidase studies. The stroma between nodules of endothelial cells was fibrotic with a mixed inflammatory infiltrate of lymphocytes, plasma cells, histiocytes, and occasional eosinophils (Figure 3).

This large splenic tumor is a neoplasm of partially epithelioid endothelial cells forming nodules of irregular vascular spaces. Vascular spaces are poorly formed centrally and surrounded by epithelioid endothelial cells, imparting a granulomatous appearance. Intervening stroma has a mixed inflammatory infiltrate and fibrosis. The slow growth is manifested by the central sclerosis and calcification. Overall features are those of a hemangioendothelioma, a tumor more commonly seen in soft tissue, liver, lungs, or bone. In fact, to my knowledge, no previous example of hemangioendothelioma in the spleen has been described.

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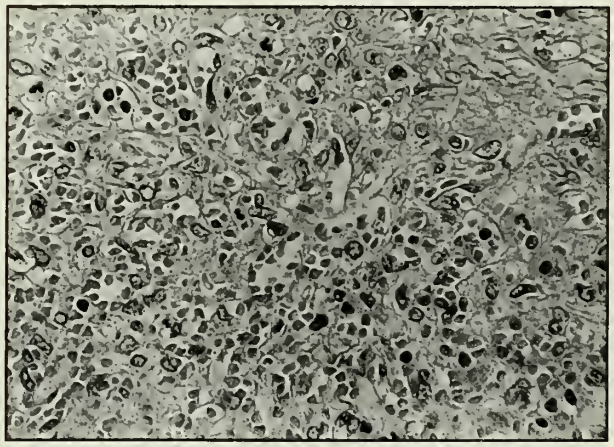

Figure 3.—On light microscopy, the irregular dark nodules seen grossly were composed of endothelial cells forming slit-like vascular spaces filled with erythrocytes (hematoxylin and eosin stain, original magnification × 250).

Hemangioendotheliomas are vascular tumors of endothelial origin midway between benign hemangiomas and angiosarcomas. Because of the epithelioid appearance of endothelial cells, these tumors can be mistaken for carcinoma or melanoma. Careful evaluation to identify the vasoformative cell pattern or immunoperoxidase studies to identify factor VIII are needed to recognize the true nature of these neoplasms. The behavior of the tumors varies greatly according to site of origin. In an organ such as the spleen that can be removed entirely, recurrence is unlikely. In other organs, such as bone, where the tumor is often multifocal, slow progression can occur. Surgical excision is the treatment of choice when possible.

The interpretation of this splenic nodule as an inflammatory pseudotumor was a reasonable diagnosis before histologic examination. Hemangioendotheliomas often have an inflammatory appearance, as this one does. When seen in soft tissue, the terms "angiolymphoid hyperplasia with eosinophilia" and "pseudopyogenic granuloma" have been used.

Histologic Diagnosis

Hemangioendothelioma of the spleen.

DR DRACHMAN: John Kirkpatrick, MD, has been the patient's primary care physician throughout his course. He will describe the patient's clinical condition since the surgical procedure.

JOHN KIRKPATRICK, MD*: The patient was discharged on the fifth postoperative day after an uneventful operation, except that his platelet count had risen to 603×10^9 per liter (603,000 per mm^3). He was readmitted a week later because of crampy lower abdominal pain and bloody stools. His platelet count on this admission was 975×10^9 per liter (975,000 per mm^3). A flexible sigmoidoscopy showed changes consistent with ischemic colitis; the patient was treated with hydroxyurea for this "postsplenectomy thrombocytosis." He was discharged after only one day, and on follow-up his platelet count has gradually diminished. At his three-month postoperative visit, his platelet count was 494×10^9 per liter (494,000 per mm^3), his hematocrit was 0.45 (45%), hemoglobin level was 146 grams per liter (14.6 grams per dl), and the ESR was 1 mm per hour. His energy has returned to normal, and he has not had any infectious complications. At this point, there is no evidence of recurrent or residual disease.

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Acknowledgment

Juan Rosai, MD, Memorial Sloan-Kettering Cancer Center, New York City, reviewed the pathology report. Important clinical information was provided by Elizabeth Peralta, MD, and John Ryan, MD, of the Virginia Mason Hospital.

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Epitomes

Important Advances in Clinical Medicine

Ophthalmology

Alfred C. Marrone, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in ophthalmology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Ophthalmology of the California Medical Association, and the summaries were prepared under the direction of Alfred C. Marrone, MD, and the panel.

Keratorefractive Surgery

"KERATOREFRACTIVE" OR "REFRACTIVE" SURGERY refers to the overall family of procedures that permanently alter the way the eye refracts incoming light. Each procedure achieves its effect by altering the curvature of the cornea. To diminish myopia (nearsightedness), the cornea is flattened. To diminish hyperopia (farsightedness), the cornea is steepened. To diminish astigmatism, the cornea is flattened in the axis of the steeper corneal curvature. The hyperopic procedures, using automated lamellar keratoplasty or the excimer laser, are not as widely done as the myopic and astigmatic procedures. Although there are many forms of keratorefractive surgery, the most common are radial keratotomy, astigmatic keratotomy, automated lamellar keratoplasty, and photorefractive keratectomy using the excimer laser. These procedures are often combined to achieve optimal results.

Patients seek refractive surgery because they wish to see well without physical dependence on glasses or contact lenses, especially in emergency situations, to improve their performance in a profession or sport, or to meet the visual requirements for occupations such as law enforcement or fire fighting. A person with high myopia who cannot tolerate contact lenses may be severely visually handicapped by the need to wear spectacles that diminish the image size and may grossly distort image quality. These patients seek permanent surgical reduction of myopia simply to be able to function in everyday activities.

Radial keratotomy has been done in the United States since 1978 and involves making deep radial incisions into the corneal stroma, leaving a clear central "optical" zone around the pupil into which no incisions are made. Usually four or eight radial incisions are created using a handheld diamond scalpel. Radial keratotomy is effective in diminishing nearsightedness of 6.00 diopters (D) and below, but higher amounts of nearsightedness can be corrected in patients in their 40s or 50s. In radial keratotomy, about 10% to 25% of patients require a second operation to achieve the final result. The Prospective Evaluation of Radial Keratotomy (PERK) Study, sponsored by the National Eye Institute, found that 92% of patients with low myopia (between 1.50 and 3.00 D) and 86% of patients with myopia between 3.12 and 6.00 D had a visual acuity of 20/40 or better without spectacles or contact lenses five years after the operation. The PERK study serves as a valuable benchmark for evaluating other studies and the results of other keratorefractive surgical procedures.

Astigmatic keratotomy can be done alone or, most commonly, in combination with radial keratotomy, during or after cataract surgery, or following automated lamellar or penetrating keratoplasty to diminish astigmatism. This consists of making transverse or arcuate incisions in the peripheral cornea in the axis of the steeper corneal curvature. These incisions are effective in diminishing astigmatism from 1.00 to 4.00 D.

Automated lamellar keratoplasty is starting to be used to correct high amounts of nearsightedness from about −6.00 to −30.00 D. Although it can also be used to correct low hyperopia from +1.00 to +5.00 D, most clinical experience with this procedure is in correcting myopia rather than hyperopia. In automated lamellar keratoplasty, a motorized microkeratome using a steel blade creates a lamellar dissection of a one-third-thickness hinged corneal flap overlying the pupil. The corneal flap is folded back, and a second pass of the microkeratome permanently removes a central lamellar disc of corneal stroma, the thickness of which is determined by the degree of myopia. The hinged flap is then laid back in place and attaches to the underlying stroma by capillary attraction without the use of sutures. The cornea heals rapidly with minimal discomfort. As with radial keratotomy, the exact postoperative refraction is not entirely predictable for each patient. In a multicenter study involving 100 eyes, 75% of eyes of patients with high myopia achieved vision

of 20/40 or better without the use of spectacles or contact lenses. In this study, 25% of patients required radial keratotomy and 5% required astigmatic keratotomy a few months after the keratoplasty to "fine-tune" the procedure and achieve the final results.

Photorefractive keratectomy is a surgical procedure that recontours the anterior surface of the cornea using 193-nm UV light from the argon fluoride excimer laser. A central circular zone of cornea measuring 4 mm to 6 mm overlying the pupil is ablated. The depth of ablation is determined by the amount of myopia. Although the excimer laser is used widely throughout the world, in the United States clinical trials under the auspices of the Food and Drug Administration (FDA) are currently underway. The excimer laser may soon be approved by the FDA for the treatment of corneal opacities in eyes with corneal scarring or corneal dystrophy, but the FDA must still decide whether or not to approve the procedure for the correction of refractive errors in healthy eyes.

Thus far, studies have shown that the excimer laser is as effective as radial keratotomy in diminishing nearsightedness as high as 6.00 D. Between 88% and 91% of patients demonstrate a visual acuity of 20/40 or better without glasses or contact lenses. As with radial keratotomy, patients with lower amounts of preoperative myopia achieve better results. Repeated operations for undercorrection or scarring will be needed in as much as 14% of treated eyes. Repeated procedures are far more common in eyes with higher preoperative myopia (>6.00 D). Complications such as the reduction of vision due to glare, undercorrection, or overcorrection appear to be no more common than after radial keratotomy. The regression of effect tends to be more common than with radial keratotomy, however, especially when refractions exceed −6.00 D. These problems may be diminished by using larger ablation zones (6 mm). The excimer laser can be combined with automated lamellar keratoplasty to treat high myopia. This protocol is currently being studied by the FDA and is showing favorable results.

Each of the refractive surgical procedures discussed is highly effective for permanently reducing nearsightedness and astigmatism. The final refraction for a patient is not entirely predictable, however. This is why second operations are required for 10% to 25% of patients undergoing each procedure. Although no refractive surgical procedure is without vision-threatening complications, the incidence following radial keratotomy, automated lamellar keratoplasty, and photoreactive keratectomy is low. Persistent symptoms such as glare, halo or starburst effect, occasional foreign body sensation, undercorrection, and overcorrection can be troublesome, but generally are not vision-threatening. A concern with radial keratotomy is the tendency of 15% to 20% of patients to have a continued flattening of the cornea years after the procedure. This can result in hyperopia, so most surgeons leave the eye slightly myopic after the procedure. Radial keratotomy and photorefractive keratectomy seem to be equally effective for correcting myopia below −6.00 D. Automated lamellar keratoplasty alone or combined with photorefractive keratectomy is effective in diminishing myopia above −6.00 D.

When selecting and counseling a patient for keratorefractive surgery, careful consideration must be given to the patient's expectation for visual result and the person's specific requirements for uncorrected visual acuity. Although patients with unrealistic expectations should be discouraged from having surgical therapy, those who wish to diminish their dependence on spectacles or contact lenses or who require better uncorrected vision for occupational or avocational needs can benefit from refractive surgery.

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Updated Recommendations From the Optic Neuritis Treatment Trial

ANALYSIS OF DATA from the Optic Neuritis Treatment Trial (ONTT) has resulted in new recommendations for the management of optic neuritis. Whereas initial reports suggested a modest improvement in visual function at six months after a course of intravenous methylprednisolone sodium succinate followed by oral prednisone, one-year follow-up disclosed no notable difference between treated patients and controls. Therapy did, however, result in more rapid improvement of optic nerve function during the first several weeks after the onset of symptoms. Current practice, therefore, is to treat for visual effect only if there is a need to speed early recovery, as in patients with one functioning eye and those who need to recover binocularity quickly for occupational reasons. Oral prednisone therapy alone leads to an increase in the recurrence rate for optic neuritis, and this therapy remains contraindicated for typical cases.

Initial reports suggested no notable value for diagnostic studies such as serologic testing and magnetic resonance imaging (MRI) of the brain in routine cases. This stance has been altered based on newer information. Patients who had abnormal MRI scans, defined by the presence of two or more white-matter lesions of at least 3 mm in diameter, had significantly higher risk (36% versus 3% for those with no lesions) for multiple sclerosis developing within two years. When treated with intravenous methylprednisolone followed by oral prednisone, these patients showed a significantly lower rate of new neurologic events consistent with multiple sclerosis (7.5% versus 16.7% in placebo-treated patients) developing at two

years. The Optic Neuritis Study Group thus recommends MRI of the brain in all patients with acute optic neuritis, with intravenous and subsequent oral corticosteroid therapy instituted for those with abnormal scans.

The cost and the use of hospital resources are important disadvantages of intravenous therapy if provided in the typical inpatient setting with divided daily doses. With the safety of this form of short-term treatment demonstrated by the ONTT, consideration may be given to administering the intravenous medication once a day (1 gram bolus) on an outpatient basis. Such a regimen has long been in use for patients having chemotherapy and following organ transplantation and is being adopted more frequently by neuro-ophthalmologists.

The ONTT has provided a wealth of information about optic neuritis and its relation to multiple sclerosis. Findings related to oral steroid effects on the recurrence rate and intravenous steroid effects on the development of multiple sclerosis are as yet not well explained, even if borne out empirically. They remain controversial, and the long-term investigation of these and other aspects of optic neuritis therapy, such as the optimal steroid dosage, the timing of treatment, and the management of recurrences, continues.

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Do Sunglasses Protect the Retina From Light Damage?

Opinions on the need for wearing sunglasses range from "All eyes should be protected from sunlight from a young age" to "Healthy eyes do not need sunglasses." What is the best evidence to guide us in answering patients' questions about wearing sunglasses?

In sunlight, the wavelengths of light that seem most damaging to the eye are blue (400 to 500 nm), UV A (320 to 400 nm), and UV B (290 to 320 nm). In youngsters, both the lens and the retina receive relatively large amounts of these short-wavelength radiations because the lens transmits most of them to the retina. In adults, the vast majority of blue and UV radiation is absorbed by the lens, and this has been associated with cataract formation. Furthermore, the incidence of pterygia and age-related macular degeneration has been shown to be higher in men who work in waterways (such as Chesapeake Bay) than on age-related matched controls. This may be related to blue or all visible wavelength light. Also, it has been suggested that "indoor" illumination, involving short-wavelength energy, can play a role in total damage to the retina. Aphakic eyes are more at risk for UV damage, and currently almost all the nonsilicone intraocular lenses used in cataract surgery absorb UV light. Eyes in which the pupils cannot constrict in response to bright light are also more at risk for light damage.

Most sunglasses do a good job of blocking UVB radiation. The transmission of UVA, however, can be as high as 75% in some sunglasses, so UVA-blocking characteristics must be specified if total UV protection is desired. To ensure complete UV protection, this should be specifically requested at the time of purchase. It is not necessary to buy darkly tinted lenses to obtain protection from UV and blue light. It is possible to block essentially all UV radiation with clear lenses. Yellow, orange, or brown tints may be selected to block blue wavelengths.

Those most at risk for retinal damage from short-wavelength light are patients with aphakia or pseudophakia with a non–UV-absorbing intraocular lens because there is nothing except the cornea in front of the retina to absorb the energy. Also at increased risk may be children, with their clear lenses; persons whose eyes have nonconstricting pupils; and persons with long-term exposure to high light levels. In general, it seems prudent to protect the retina from exposure to blue and UV wavelength light. This may also result in a decreased incidence of cataracts and pterygia.

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Nonsteroidal Eye Drops for Ocular Allergy

Seasonal allergic conjunctivitis is a common ocular condition affecting all age groups. Salient symptoms include itching, epiphora (tearing), and erythema. Although allergic conjunctivitis responds to topical corticosteroids, the use of these medications can have serious complications including cataract and glaucoma. Corticosteroids should be used rarely, if at all, in the management of allergic eye disease. They should be prescribed only by an ophthalmologist and only for extremely resistant cases. Hence, the search for additional topical medications for seasonal allergic conjunctivitis has continued.

During the past 18 months, three new topical, nonsteroidal, ophthalmic preparations for treating allergic conjunctivitis and related diseases, such as atopic keratoconjunctivitis and vernal keratoconjunctivitis, have become commercially available.

The first of these three is ketorolac tromethamine 0.5% (Acular). Ketorolac is a nonsteroidal, topical anti-inflammatory preparation approved by the United States Food and Drug Administration for allergic conjunctivitis. In a recent double-blind clinical trial, this medication has been shown to be effective for the treatment of allergic keratoconjunctivitis, especially compared with placebo (a

strong placebo effect was seen in the clinical trials). The use of this medication has been reported previously in clinical studies of patients with allergic conjunctivitis. Ketorolac is an alternative to an antihistamine-vasoconstrictor combination that has been commercially available, and its use has been shown to relieve conjunctival inflammation, itching swollen eyes, burning, tearing, foreign body sensation, and photophobia. This drug is expensive, however, and has a side effect of substantial stinging for some patients. Its improvement over the commercially available antihistamine-vasoconstrictor combination has yet to be established.

Lodoxamide 0.1% is a mast cell stabilizer and prevents the release of mast cell mediators such as histamine. This newly available topical pharmaceutical is 2,500 times more active than cromolyn sodium in inhibiting the passive cutaneous anaphylactic reaction in animal models. Cromolyn sodium has been documented to be safe and effective in the management of vernal keratoconjunctivitis, but this drug is no longer commercially available in the United States. Lodoxamide has been approved for use for vernal keratoconjunctivitis, an uncommon form of type IV hypersensitivity that is probably related to allergic conjunctivitis. Lodoxamide was documented to be safe when used four times a day for as long as 28 days with few side effects, although some patients complained of burning sensations. Lodoxamide has not yet been shown to be effective in allergic conjunctivitis, but logically may be of some assistance. It requires about two weeks to establish an effective level since stabilization of mast cells will only prevent future symptoms and will not relieve or block the histamine that has already been released.

Levocabastine hydrochloride 0.05% is a potent histamine (H_1) antagonist. This topical nonsteroidal histamine antagonist has recently been made available for ocular use in allergic conjunctivitis. Patients with seasonal allergic conjunctivitis have a tenfold increase in histamine levels in their tears compared with patients without allergic signs and symptoms. Levocabastine is a synthesized histamine antagonist that has been formulated as either an ocular preparation or a nasal spray. It is one of the most potent antihistamine-histamine compounds available and is at least 15,000 times more potent than chlorpheniramine. Its use has been found to be safe and effective, particularly on days when the pollen count was high. The drug is well tolerated, and its use decreases subjective symptoms of irritation, pain, and tearing.

Initial studies with levocabastine compared it with another orally administered antihistamine for the prophylaxis and treatment of seasonal rhinoconjunctivitis. In the available findings, levocabastine was either superior to or similar to other antihistamines in the prophylactic treatment of seasonal rhinoconjunctivitis. Although levocabastine has been compared with other antihistamines and has been found to be an effective ocular medication for seasonal allergic conjunctivitis, it has not been compared with the currently available topical antihistamine-vasoconstrictor combination. Levocabastine has minimal side effects except for occasional stinging. It is relatively expensive: suggested retail is between $23 and $29 for 5 ml.

None of the three pharmaceutical agents has been compared with the currently available antihistamine-vasoconstrictor combination and may be only minimally more effective. The standby therapy for allergic conjunctivitis consists of cold soaks, lubrications including artificial tears, and oral or, occasionally, topical antihistamines. If the condition is recurrent and severe, antigen testing and desensitization may be considered. Vernal keratoconjunctivitis or perhaps atopic keratoconjunctivitis may be best managed with lodoxamide. An H_1 blocker or nonsteroidal anti-inflammatory drug may also be of assistance in some selected cases.

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Risk of Corneal Infection and Extended Wear of Contact Lenses

CORNEAL MICROBIAL INFECTION is probably the most feared complication of wearing contact lenses. Both scientific study and a century of clinical experience with these devices suggest that corneal infection is a relatively rare event when contact lenses are restricted to daily (open-eye) wear and when compliance with care techniques and hygiene is good. Extending contact lens wear through one or more sleep cycles—extended wear—over the past two decades has dramatically increased the incidence of associated corneal infection. Wearing contact lenses, especially extended wear, is now considered a major risk factor for corneal infection, and all varieties of contact lenses—soft (both disposable and reusable), rigid gas permeable, and other less common types—have been involved.

The microorganisms associated with contact lens-related corneal infections include principally *Pseudomonas* species, particularly *Pseudomonas aeruginosa*, and *Staphylococcus* species, although other bacteria, fungi, and *Acanthamoeba* species have occasionally been identified in the lesions. (Infections with *Acanthamoeba* species have been associated more with poor contact lens care and daily wear than extended wear.) It is thought that the microtrauma of lens wear and care, improper lens maintenance, chronic hypoxia, and perhaps some form of suppression of ocular surface immunity participate in producing infection, but our understanding of the infectious process remains incomplete.

To minimize the risk of contact lens-associated keratitis (and other complications such as corneal abrasion,

neovascularization, and giant papillary conjunctivitis), wearers should take the following steps:

- Use contact lenses solely for daily (open-eye) wear;
- Never sleep or nap with contact lenses on the eyes;
- Care for contact lenses in a manner consistent with guidelines authorized by both the manufacturer and the United States Food and Drug Administration and common concepts of good hygiene (such as always washing hands before manipulating a lens, and not rinsing contact lenses in tap water before insertion);
- Obtain professional supervision at scheduled intervals to ensure that mechanical, optical, and physiologic responses are regularly monitored and optimized—even if there are no symptoms; and
- If experiencing ocular discomfort, pain, foreign body sensation, discharge, photophobia, or red eyes, immediately remove the contact lens. Should these signs or symptoms persist more than a few minutes, the patient should be professionally examined that day.

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Alerts, Notices, and Case Reports

Lysis Pneumonopathy Associated With the Use of Fludarabine Phosphate

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RAPIDLY PROGRESSIVE RESPIRATORY FAILURE is an uncommon manifestation of the systemic tumor lysis syndrome. In this report, we provide the first description of "lysis pneumonopathy" following treatment with fludarabine phosphate, a nucleoside analogue recently approved by the United States Food and Drug Administration. The rapid cell death that may occur following therapy for lymphoid malignancy with newer antimetabolites has resulted in unexpected syndromes of tumor lysis.[1-3] To date, reports of diffuse alveolar damage due to tumor lysis are rare and limited to patients with massive tumor burden in the chest susceptible to systemic chemotherapy.[4-6] Such heavy pulmonary involvement, however, is common with slow-growing lymphoid cancers. Thus, with the expanded use of antimetabolites such as fludarabine and 2-chlorodeoxyadenosine, a growing number of patients may be at risk for pulmonary complications of tumor lysis. The case reported here is presented to alert clinicians to a possible occurrence of lysis pneumonopathy as the clinical indication for purine analogues expands to include low-grade lymphoid tumors with extensive mediastinal and pulmonary involvement.

Report of a Case

The patient, a 43-year-old man, was referred to the Department of Veterans Affairs Medical Center outpatient clinic for the treatment of a stage 4, low-grade (well-differentiated lymphocytic) lymphoma. The patient, originally diagnosed with lymph node and bone marrow involvement, had been treated in the previous six years with numerous combinations of chlorambucil, prednisone, cyclophosphamide, and vincristine sulfate, yet his tumor slowly progressed. He had chronic but stable dyspnea and generalized lymphadenopathy with hepatosplenomegaly.

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An abdominal computed tomographic scan revealed massive retroperitoneal lymphadenopathy without hydronephrosis. Although the patient had refused another bone marrow biopsy, his tumor had displayed no clinical or laboratory evidence suggesting transformation to a more aggressive form (such as Richter's syndrome). His chest radiograph showed bilateral interstitial nodular markings in the lower lung fields and a stable left-sided pleural effusion diagnosed by thoracentesis as chylous and thought to be precipitated by massive mediastinal tumor involvement. Laboratory studies revealed a leukocyte count of 8.7×10^9 per liter (8,700 per mm^3) with 0.52 (52%) normal-appearing lymphocytes and no immature forms, a hemoglobin level of 132 grams per liter (13.2 grams per dl), a platelet count of 205×10^9 per liter (205,000 per mm^3), and the following serum values: potassium, 4.3 mmol per liter; bicarbonate, 25 mmol per liter; creatinine, 106 μmol per liter (1.2 mg per dl); phosphate, 1.36 mmol per liter (4.2 mg per dl); and calcium, 2.42 mmol per liter (9.7 mg per dl). Serum uric acid and lactate dehydrogenase levels were not obtained.

The oncology service was consulted and, following verbal informed consent, a five-day outpatient course of fludarabine phosphate (25 mg per m^2 a day) was initiated. Allopurinol (300 mg a day) was prescribed, but the patient was not instructed to increase his fluid intake. After only two days of therapy dyspnea, cough, and a low-grade fever developed, accompanied by bilateral (right greater than left) alveolar-type densities on chest radiograph (Figure 1). Fludarabine therapy was discontinued. Arterial blood gas determinations obtained while the patient was using a non-rebreathing mask (fraction of inspired oxygen ≥ 0.8%; barometric pressure, 690 mm of mercury) showed a pH of 7.42, a P_{O_2} of 69 mm of mercury, and a P_{CO_2} of 33 mm of mercury. Following admission, his oxygenation rapidly deteriorated, necessitating intubation and mechanical ventilatory support. The platelet count was 210×10^9 per liter (210,000 per mm^3), and there was no laboratory evidence of disseminated intravascular coagulation. Empiric treatment with intravenous hydration, the combination drug trimethoprim and sulfamethoxazole, erythromycin, and methylprednisolone sodium succinate was initiated. The following day, a video-assisted thoracoscopic right lung biopsy was done that revealed diffuse alveolar damage with occasional abnormal aggregations of lymphoid cells. There was minimal alveolar hemorrhage and no vascular obstruction (Figure 2). The results of all stains (Gram's, Gomori's, methenamine silver, methylene blue, *Legionella pneumophila* direct fluorescent antibody, and acid-fast) and cultures (routine bacterial, mycobacterial, fungal, and cytomegaloviral) were negative, and antibiotic therapy was discontinued. Laboratory studies done that day revealed evidence of

Figure 1.—**Left**, A chest radiograph obtained at the time of admission reveals bulky mediastinal, hilar, and peritracheal adenopathy, a left pleural effusion, and bilateral (right greater than left) alveolar and interstitial markings. A subsequent portable chest radiograph revealed progression of the alveolar pattern to include both lungs in a similar manner. **Right**, A chest radiograph obtained 2 months after admission reveals reduced adenopathy and resolution of the alveolar infiltrates.

tumor lysis with a potassium level of 5.8 mmol per liter; bicarbonate, 19 mmol per liter; creatinine, 106 μmol per liter (2.1 mg per dl); phosphate, 2.55 mmol per liter (7.9 mg per dl); calcium, 1.72 mmol per liter (6.9 mg per dl); and uric acid, 970 μmol per liter (16.4 mg per dl).

During the first two days of the patient's hospital stay, his fluid intake had exceeded output by only 800 ml. The right atrial pressure was 11 mm of mercury, pulmonary artery wedge pressure was 16 mm of mercury, and the cardiac output was 8.53 liters per minute. He was treated with a regimen of furosemide, acetazolamide, allopurinol, and intravenous fluids as needed. His arterial blood gas measurements progressively improved, and the chest radiographic abnormalities resolved (Figure 1). He was extubated on the fifth hospital day, and his metabolic indicators of tumor lysis returned to normal by hospital day 8.

Five months later, the patient's adenopathy had recurred, and fludarabine was given concurrently with prednisone, hydration, and allopurinol. This time, he had no adverse pulmonary sequelae or biochemical evidence of tumor lysis.

Discussion

The development of acute renal failure, hyperuricemia, hyperphosphatemia, and hypocalcemia associated with a reduction in adenopathy supports the diagnosis of the tumor lysis syndrome in this patient. Although tumor lysis is most common following therapy for rapidly proliferating cancers, it has recently been reported in patients with chronic lymphocytic leukemia who were treated with fludarabine[1,2] or 2-chlorodeoxyadenosine.[3]

Pulmonary injury precipitated by rapid tumor breakdown is not a commonly reported manifestation of the systemic tumor lysis syndrome. Lysis pneumonopathy, however, appears to be more frequent following successful chemotherapy in patients with heavy pulmonary or mediastinal tumor burdens.[4-6] In these cases, diffuse alveolar damage occurs, and the clinical presentation is consistent with noncardiac pulmonary edema–associated acute respiratory failure. Unlike other causes of the adult respiratory distress syndrome, lysis pneumonopathy commonly resolves with aggressive respiratory support and with treatment of the tumor lysis syndrome.[4]

Fludarabine-induced depletion of $CD4^+$ T lymphocytes may predispose patients to the development of pneumonitis due to opportunistic infections.[7,8] The lack of demonstrable pathogens on direct stains and cultures of pulmonary tissue makes infectious pneumonitis an unlikely cause in this case. Likewise, many who are given fludarabine, including this patient, have previously received alkylating agents known to be associated with pulmonary toxicity.[9] Enhanced pulmonary injury resulting from synergism between alkylating agents and fludarabine has not been described. This patient had no history of recurrent fevers or cough and lacked alveolar fibrosis. Such findings are common with cyclophosphamide- or chlorambucil-induced pulmonary toxicity,[9] and their absence suggests that preexisting cytotoxic pulmonary damage had not occurred. Direct pulmonary injury, in the form of diffuse alveolar damage[10] or interstitial pneumonitis,[11-13] has been reported with the use of fludarabine. Such drug-induced pulmonary toxic effects typically have occurred after several courses of fludarabine. Although we cannot exclude direct fludarabine toxicity in this case, the onset of respiratory distress within two days of therapy, the temporal association with systemic tumor lysis, and the successful rechallenge present a clinical scenario much more consistent with lysis pneumonopathy.

Figure 2.—A video-assisted thoracoscopic lung biopsy specimen was taken from the right lung on the second hospital day. Histologic examination reveals edematous alveolar septa with some flooding of alveolar spaces with macrophages. Early hyaline membranes are seen (hematoxylin and eosin stain, original magnification × 200).

The mechanism responsible for diffuse alveolar damage in association with systemic tumor lysis is unknown. In the few reports to date, chemotherapy-susceptible tumor burden involving the lung and mediastinum appears essential. Indeed, rapid tumor cell death resulting in the obstruction of pulmonary microvessels has been clearly associated with the development of endothelial and alveolar cell injury even in the absence of the systemic tumor lysis syndrome.[14,15] It has been postulated that locally released cell constituents mediate this pulmonary damage.[16] Traditional nucleoside antimetabolites, such as cytosine arabinoside, may precipitate similar episodes of noncardiac pulmonary edema that may, in part, be triggered by intrapulmonary cell lysis.[17] Thus, the use of fludarabine, which is highly active against slow-growing lymphoid cancers, may result in an occurrence of pulmonary toxicity associated with tumor lysis.

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Massive Hemoptysis in Pregnancy Due to a Solitary Pulmonary Arteriovenous Malformation

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MASSIVE HEMOPTYSIS, variably defined as 100 to 600 ml of expectorated blood in 24 hours, is a possibly fatal event[1,2] rarely reported during pregnancy.[3] We recently saw a 25-year-old woman in her seventh month of pregnancy who was found to have a solitary pulmonary arteriovenous malformation as the cause of massive hemoptysis. The presence of the lesion was suggested by a two-dimensional contrast echocardiogram.

Report of a Case

The patient, a 25-year-old gravida 1 para 0 woman at 33 weeks' gestation, was seen because of a history of recurrent hemoptysis. She said that she had coughed up between one and two cups of blood on ten occasions in the two weeks before this evaluation. She did not have fever, chills, or purulent sputum. Although there was no history of dyspnea or chronic fatigue before her pregnancy, she had recently noted substantial shortness of breath.

Her medical history was remarkable only for three episodes of bronchitis or pneumonia, which had resolved with antibiotic therapy, and one episode of blood-tinged sputum at least a year before her pregnancy. Her family history was unremarkable. After an initial evaluation by an otolaryngologist, who found no evidence of bleeding or disease in the upper airways, the patient was referred to the pulmonary clinic.

On physical examination the patient had pronounced pectus excavatum and crackles in the mid-left lung field. There were no skin or mucosal telangiectasias. Clubbing and cyanosis were absent, and the examination elicited no further abnormalities. Her chest radiograph showed dense consolidation of the lingula (Figure 1). A comparison film from 18 months earlier had been interpreted as normal. Fiberoptic bronchoscopy revealed active oozing from the lingula but no endobronchial lesions. After the procedure, the patient expectorated about 150 ml of blood, and mild hypoxemia developed. Supplemental oxygen was provided, and the hypoxemia resolved over several hours.

The patient was admitted to the labor and delivery ward for close monitoring, empiric antibiotic therapy, and further investigation. Recurrent hemoptysis over the next 24 hours resulted in an additional 150 ml of blood loss and transient hypoxemia. Her hematocrit dropped from an admission level of 0.34 to 0.26 (34% to 26%). She was given betamethasone to speed fetal lung maturation, and the induction of labor was planned after amniocentesis. Concern about fetal radiation exposure led to a consideration of various noninvasive, low-risk diagnostic tests, including a shunt study and contrast echocardiography to screen for vascular malformations. Her shunt fraction (a measure of blood bypassing pulmonary alveolar capillary units), calculated while breathing 100% oxygen, was elevated at 13% (normal 5%). An echocardiogram with bubble contrast demonstrated the delayed appearance of microcavitations consistent with an extracardiac right-to-left shunt.

The patient had two additional but less substantial (<100 ml) episodes of hemoptysis before delivery. Labor was successfully induced at 35 weeks, and a healthy baby was delivered vaginally. The following day the patient underwent pulmonary arteriography. A pulmonary arterio-venous malformation measuring 1 cm was found in the lingula (Figure 2) and was successfully embolized with steel coils (Figure 3). A chest computed tomographic (CT) examination was done to search for additional vascular lesions, but none were found. Contrast echocardiography was repeated, but showed no evidence of shunt. Nine months later the patient had had no further hemoptysis. Her chest radiograph was normal except for the presence of the wire coils and pectus excavatum.

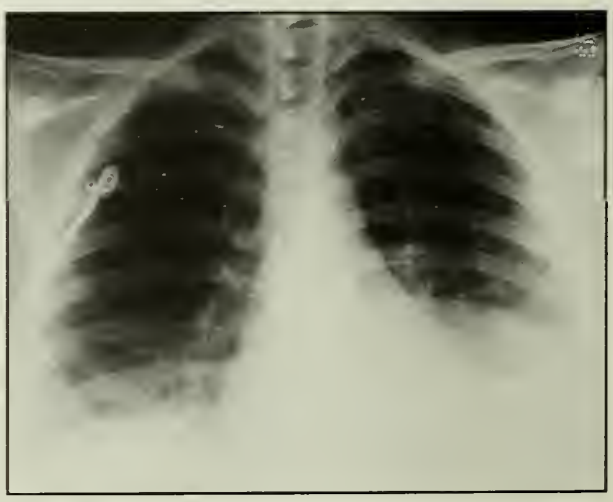

Figure 1.—An anteroposterior chest radiograph at the time of admission shows obliteration of the left side of the heart border due to lingular consolidation.

(Bradshaw DA, Murray KM, Mull NH IV: Massive hemoptysis in pregnancy due to a solitary pulmonary arteriovenous malformation. West J Med 1994; 161:600-602)

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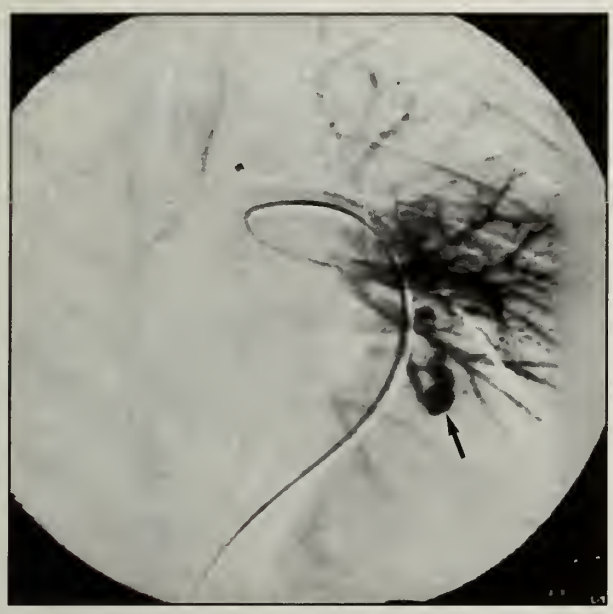

Figure 2.—Digital subtraction angiography shows arteriovenous malformation in the left lung, which corresponds to the site of bleeding identified bronchoscopically and on chest radiograph.

Discussion

Although many patients with pulmonary arteriovenous malformation are asymptomatic, life-threatening complications have been well documented, including hypoxemia, hemothorax, brain abscess, stroke, and hemoptysis.[4,5] Hemoptysis was reported to occur in 6 (10%) of 63 patients with pulmonary arteriovenous malformation in one series[6] and in 10 (13%) of 76 in another series.[7] The cardiovascular effects of pregnancy, including an increase in blood volume and cardiac output[8] and hormonally related vascular changes,[9] may adversely affect vascular malformations. Previously reported complications of the disorder in pregnancy include hemothorax in four patients[10-12] and worsening hypoxemia due to shunt in one.[13] Our report, however, is the first to describe hemoptysis due to a pulmonary arteriovenous malformation in pregnancy. In addition, our patient had no historical or physical evidence of hereditary telangiectasia, which is said to increase the incidence of complications associated with this disorder.[14] In fact, four of the six previously reported pregnant women with this disorder had hereditary telangiectasia,[10,11,13] and no details were given in the other two cases.[12]

The evaluation of massive hemoptysis focuses first on promptly identifying the site of bleeding.[1] In our patient, the bleeding site was located in the lingula at bronchoscopy. Chest CT and angiography, beginning with the bronchial circulation (the source of most hemoptysis), are often necessary to establish a precise diagnosis. These procedures may be associated with substantial radiation exposure to the fetus of a pregnant patient, however. Magnetic resonance imaging has been successfully used in the diagnosis of pulmonary arteriovenous malformations[15] and was done on our patient. Unfortunately, the location of the lesion near central vessels as well as cardiac motion artifact probably contributed to a nondiagnostic study.

Two-dimensional echocardiography with the administration of a saline solution has been reported to be extremely valuable in detecting pulmonary arteriovenous malformations.[16] This technique involves the rapid intravenous administration of an agitated saline solution while directly visualizing the right and left heart chambers. The appearance of microbubbles in the left atrium confirms a right-to-left shunt. When bubbles are detected in the left atrium within three cardiac cycles of their appearance in the right side of the heart, a septal defect is suggested. Delayed appearance, as occurred in our patient, provides evidence for an extracardiac shunt. A pulmonary arteriovenous malformation was subsequently confirmed by selective angiography of the pulmonary circulation. This approach kept the radiation exposure to our pregnant patient to a minimum.

The optimal management of a patient with massive hemoptysis depends on the patient's underlying condition, the cause of the hemoptysis, and the available expertise. Bed rest, a regimen of broad-spectrum antibiotics, and the judicious use of cough suppressants are often recommended as general measures. Positioning the patient with the bleeding side down to protect the uninvolved lung is also advocated. This may present a problem in a pregnant patient, whose venous return may be compromised by the gravid uterus in the right lateral decubitus and supine positions.[17] Endoscopic placement of a

Figure 3.—A postembolization angiogram shows steel coils. Flow through the arteriovenous malformation has completely stopped.

Fogarty catheter and ice saline lavage may also be useful in patients with persistent bleeding.[1]

Fortunately, most episodes of hemoptysis can be controlled with conservative management, and definitive therapy can be delayed.[18] Whereas some think that surgical resection is still the treatment of choice for most if not all anatomically circumscribed lesions,[1,2] embolization therapy using either detachable balloons[7] or steel coils[19] has been advocated by others. Embolization therapy is obviously a less invasive procedure than thoracotomy and has a high success rate in terminating active hemoptysis. The potential for recurrence, however, remains controversial. Embolization has been successfully performed during pregnancy[11] and should be strongly considered at the time of angiography.

In conclusion, pulmonary arteriovenous malformations should be considered in the differential diagnosis of hemoptysis during pregnancy. Two-dimensional echocardiography with bubble contrast is a sensitive means of detecting the disorder and is without any known risk to a pregnant woman or fetus. Pulmonary angiography can be used to confirm the findings, and embolization can then be used as definitive treatment either immediately in life-threatening cases of hemoptysis or following delivery if the patient becomes stable with conservative treatment.

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Electrocardiographic Changes Associated With Anaphylaxis in a Patient With Normal Coronary Arteries

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CLINICIANS HAVE DOCUMENTED the occurrence and have postulated mechanisms for ischemic electrocardiographic (ECG) changes during anaphylactic reactions. Coronary angiography has shown that ECG changes do not invariably correspond to underlying coronary artery abnormalities. We report the case of an older woman who, during an initially undiagnosed anaphylactic reaction, had ECG changes suggesting acute myocardial ischemia. Angiography showed normal coronary artery anatomy.

Report of a Case

A 65-year-old woman was brought to the emergency department by paramedics after she suddenly collapsed while walking down the street. When paramedics arrived, she was diaphoretic and pale; her blood pressure was 80 mm of mercury systolic, her pulse rate was 80 beats per minute, and respirations were 20 per minute. En route to the hospital, her serum glucose level was 120 mg per dl (6.7 mmol per liter).

On arrival, the patient was nonresponsive, with no spontaneous eye opening. She remained diaphoretic and pale. Her temperature was 35°C, her blood pressure was 60 mm of mercury by palpation, and her pulse rate was 126 and regular. There was no evidence of trauma to the head. Both pupils were 4 mm and reactive to light. Respirations were shallow, and no wheezing, rales, or rhonchi were heard. Examination of her heart revealed no murmur or gallop. There was no edema or cyanosis of the extremities. Femoral and carotid pulses were palpable, although radial and dorsalis pedis pulses could not be felt. Her skin was without rash or lesions. Corneal and gag reflexes were present. The Babinski response was down-going bilaterally, and the patient withdrew all four extremities to pain. She would not answer questions and did not vocalize with painful stimuli. Her rectal tone was normal. Stool was negative for occult blood.

By phone, the patient's daughter and husband reported that the patient had appeared well when she left home earlier that day. They reported a history of hypercholesterolemia and hypothyroidism. Current medications included conjugated estrogens, medroxyprogesterone

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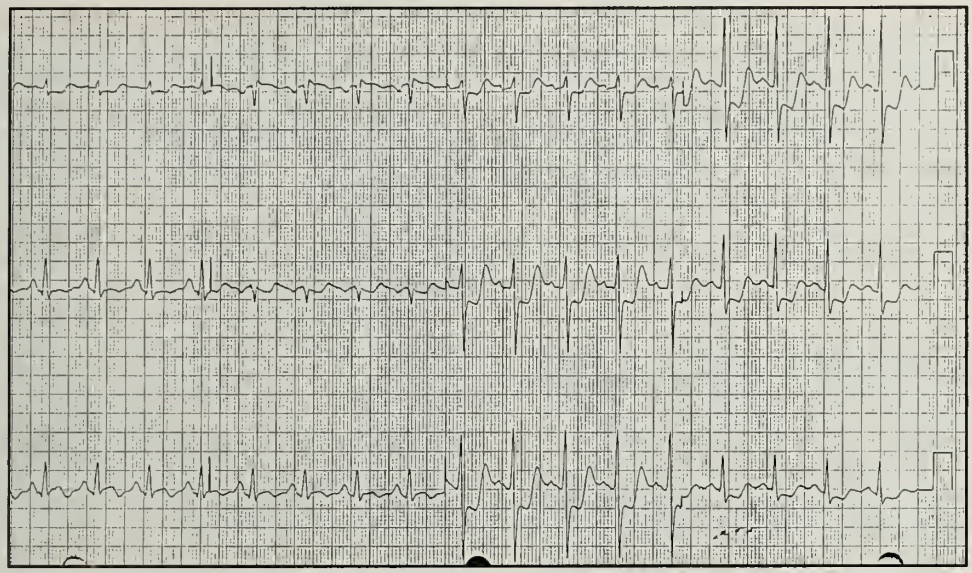

Figure 1.—The initial electrocardiogram suggests ischemia.

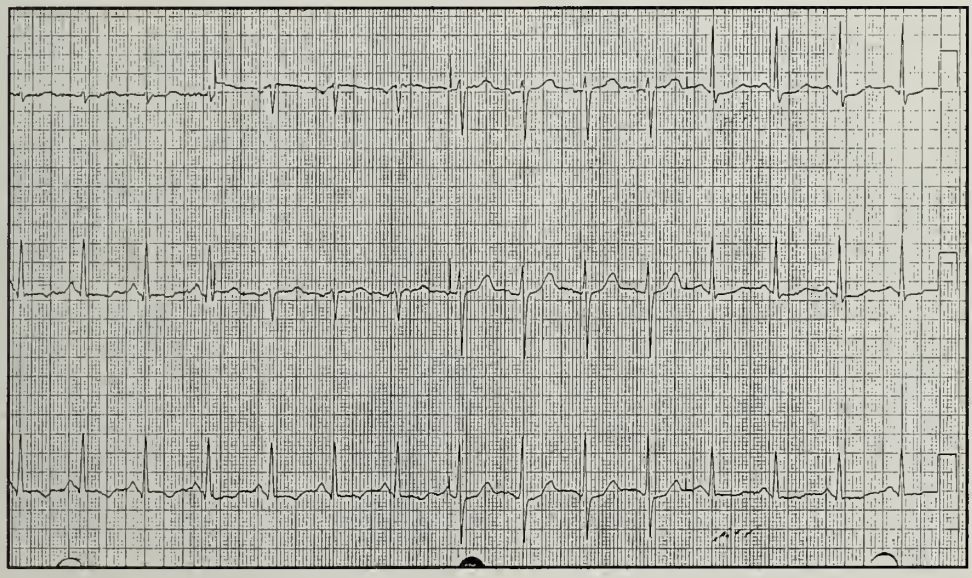

Figure 2.—A second electrocardiogram shows that the ST segments have returned to normal.

acetate, and levothyroxine sodium. The family history was pertinent for coronary artery disease in her mother and sister.

On the cardiac monitor, the patient remained in sinus tachycardia without ectopy. Changes on the ECG were interpreted as showing an acute posterior myocardial infarction (Figure 1). The following laboratory values were elicited: serum sodium, 139 mmol per liter; potassium, 3.1 mmol per liter; chloride, 108 mmol per liter; bicarbonate, 24 mmol per liter; urea nitrogen, 8.2 mmol per liter (23 mg per dl); creatinine, 106 μmol per liter (1.2 mg per dl); and glucose, 8.2 mmol per liter (147 mg per dl). The leukocyte count was 12.4×10^9 per liter (12,400 per mm^3), the hemoglobin level was 116 grams per liter (11.6 grams per dl), the hematocrit was 0.345 (34.5%), and a platelet count was 234×10^9 per liter (234,000 per mm^3). The initial creatine kinase level was 189 IU per liter, with 0.055 (5.5%) MB fractions. A chest x-ray film was normal.

After the initial ECG, a cardiology consultation was obtained. The patient received boluses of saline solution in 250-ml increments to a total of 2 liters, and dobutamine hydrochloride was added. The systolic blood pressure did not exceed 70 mm of mercury systolic. The patient's mental state improved slightly. She provided short, irritable responses to questions, and she denied having pain or other symptoms. Coronary angiography showed normal coronary artery anatomy and a left ventricular end-diastolic pressure of 11 mm of mercury. No vasospasm was seen.

Shortly after the angiogram was completed, the patient recalled being stung by a bee as she was walking to

the library. She had no previous history of allergy to bee stings. Her blood pressure was improving without further intervention, and she was given methylprednisolone sodium succinate (Solu-Medrol) and diphenhydramine hydrochloride (Benadryl) intravenously. A second ECG showed a return to normal of previous changes (Figure 2), and serial creatine kinase and MB values remained normal. After discharge the patient was referred to an allergist for Hymenoptera skin testing.

Discussion

Electrocardiographic changes consistent with acute myocardial infarction have been noted with anaphylactic reactions.[1-7] We found three reports of cases in which coronary angiography was done after anaphylaxis occurred.[1,2,8] One was in a 64-year-old man who had no history of heart disease and in whom anaphylaxis developed after he was given cefoxitin.[2] His ECG revealed acute inferior-wall injury. Serial creatine kinase enzyme levels were within normal limits. His angiography showed patent coronary arteries, although he had an anomalous origin of his right coronary artery from the left sinus of Valsalva, which possibly predisposed him to an inferior-wall myocardial injury pattern. A second case was of a patient who had an anaphylactic reaction to iodinated radiographic contrast material and had an acute inferior-wall myocardial infarction.[8] Angiography demonstrated substantial obstructive disease of the diagonal branch of the left anterior descending and distal left circumflex coronary arteries and a saccular aneurysm of the proximal right coronary artery. A third case involved a 76-year-old man with idiopathic anaphylactic shock and an ECG demonstrating acute inferolateral myocardial infarction who had angiography showing no notable narrowing of the left coronary artery, moderate stenosis of the right coronary artery, and normal left ventricular wall motion.[1] As noted, our patient had normal coronary arteries on angiography.

Our case is important because the patient had no signs of coronary artery disease on angiography but had acute ST changes on ECG consistent with a posterior myocardial infarction. Different mechanisms have been proposed to explain such changes occurring during anaphylaxis. In the past it had been postulated that the epinephrine given during an acute anaphylactic reaction caused subsequent ECG changes.[9] In our patient, ECG changes were recorded before the patient received any epinephrine. Hypoxia had been suggested in the past as a cause of the ischemic ECG changes, although studies done in intubated, well-oxygenated animals show that myocardial ischemia occurs before the bronchoconstriction seen in anaphylaxis.[6,10,11] Another proposed mechanism is vasospasm. Anaphylactic reactions of isolated perfused guinea-pig hearts show coronary vasoconstriction.[12] Different mediators causing coronary vasospasm have been proposed, including histamine, platelet-activating factor, leukotrienes C_4, D_4, and E_4, and prostaglandin SRS-A.[5,13-15] Mast cells have been found in high concentrations in atheromatous plaques.[16] Vasospasm has not been documented in humans during coronary angiography and was not seen in this patient.

This case report documents ECG changes consistent with myocardial ischemia during an anaphylactic reaction in a patient who was found at coronary angiography to have normal coronary arteries. Our patient's creatine kinase levels remained normal, and her ECG changes resolved to normal, consistent with the findings in other patients with ECG changes related to anaphylaxis and no history of coronary artery disease.

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Special Series

Dietary Antioxidants, Cancer, and Atherosclerotic Heart Disease

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Highlights

- Considerable evidence indicates that oxidative processes contribute to the development of degenerative diseases, including cancer and atherosclerotic heart disease.
- Dietary antioxidants such as vitamins C and E and β-carotene are important components of the body's defense against pathophysiologic oxidation events and, on this basis, have been proposed to protect against disease.
- Claims for the health benefits of diets rich in fruits, whole grains, and vegetables, which are naturally antioxidant-rich, cholesterol-free, and fat-poor, appear well-founded given the consistency of epidemiologic observations to this effect.
- The routine practice of antioxidant supplementation cannot be advocated on a population-wide basis because few direct prospective data of a beneficial effect have been obtained.

Antioxidants, including vitamin C, vitamin E, and β-carotene, have long been proposed to be disease-preventing agents by health activists and, more recently, have been promoted as such by members of the medical and scientific establishment. The growing interest in antioxidants stems from increasing recognition of the potentially pervasive role of oxidation in the development of diseases such as cancer and heart disease and the possibility that antioxidants may counteract disease-promoting oxidation events.[1] We provide an overview of the theoretical basis for a preventive role of antioxidants, describe studies in which this role has been examined, and consider whether currently available evidence supports claims for the health benefits of antioxidant supplementation.

Oxidants and Disease

Partially reduced forms of oxygen including superoxide (O_2^-), hydrogen peroxide (H_2O_2), the hydroxyl radical (•OH), and organic counterparts such as lipid hydroperoxides are produced during aerobic metabolism. These agents are capable of reacting with and causing oxidative injury to macromolecules including nucleic acids, proteins, lipids, and carbohydrates and thus are referred to collectively as oxidants.[1-8] Some oxidants are free radicals, which are particularly reactive due to the presence of an unpaired electron, and are capable of initiating radical chain reactions that can cause rapid spread and amplification of oxidative injury in biologic systems. Because of the possible toxicity of oxidants, numerous counteractive antioxidants have evolved to intercept and effectively deactivate these agents. The antioxidant network is not fool-proof, however, and under certain conditions such as inflammation and xenobiotic metabolism, oxidants may be produced in amounts that exceed antioxidant capacity.

Oxidative injury is suggested to be a common disease mechanism, with disease end points differing according to the identity and tissue location of the injured substrate(s). Consistent with a pervasive role in disease, oxidants have been implicated in such diverse conditions as cancer, atherosclerotic heart disease, stroke, arthritis, cataract formation, Parkinson's disease, and drug toxicity.[1-8] Because of the prevalence and the human and financial consequences of cancer and heart disease in Western societies, however, we will focus on these conditions.

Cancer

Cancer evolves from a multistage process culminating in the development and spread of cell populations that are unresponsive to the normal controls over cell proliferation.[8] DNA damage is an early event in carcinogenesis and occurs in essentially two steps: an initial DNA insult that is reparable, followed by permanent fixation of the injury, if DNA replicates before the injury is repaired.[9-11] Numerous types of modifications, including oxidation, are known to damage DNA.[12-14] Oxidative DNA damage may lead to the formation of DNA-protein cross-links, alterations in the carbohydrate backbone, or direct modifications of the purine and pyrimidine bases.[15] Oxidative

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ABBREVIATIONS USED IN TEXT

LDL = low-density lipoprotein
RDA = recommended dietary allowance

injury to DNA bases, which can result in mutations, appears to be a common occurrence in vivo. Based on determinations of urinary levels of 8-hydroxydeoxyguanosine, researchers have estimated that steady-state levels of oxidatively modified bases are as high as 10^5 in humans, with approximately 10^4 formed every day.[13,14] This occurrence rate carries with it a high likelihood that a substantial number will escape repair mechanisms and lead to a permanent change in the DNA base sequence upon replication. Oxidants also have been shown to stimulate cell proliferation[14,16,17] and thereby may promote injury fixation. Malignant tumors may develop if resulting changes in the DNA lead to the activation or altered expression of oncogenes or the inactivation of tumor suppressor genes, or both.[18-21]

The promotion of preneoplastic changes in "initiated" cells, that is, cells with alterations in the DNA that can lead to cancer, and the progression of premalignant lesions also may involve oxidants.[22-24] Because these phases occur over a much longer time frame than initiation, however, the specific events and role of oxidants are less well-defined. It is suggested that the oxidation-antioxidation potential may be particularly important in determining the "permissiveness" of the system for tumor development, in that an oxidizing environment may be more conducive for development.[22,24]

Atherosclerosis

Atherosclerosis results from the accumulation of cholesterol and the proliferation of cellular elements in the arterial wall. Considerable evidence now indicates that oxidation increases the ability of low-density lipoproteins (LDLs) to promote cellular alterations that lead to atherosclerosis.[6,7,25-39] Unlike native (nonoxidized) LDL, oxidized LDL is taken up at rapid rates by scavenger receptors on macrophages, leading to the formation of lipid-laden foam cells that form the basis of early fatty-streak lesions.[26,27] In addition, oxidized LDL may recruit circulating monocytes to the region of the developing plaque[28-30] and alter the behavior and viability of surrounding cells.[31-35]

Growing chemical and immunologic evidence supports the existence of oxidatively modified LDL in vivo.[36-39] Oxidized LDLs have been identified in atheromatous lesions,[36,37] and autoantibodies against oxidized LDL (malondialdehyde-modified LDL) have been detected in serum from both rabbits and humans.[38,39] Furthermore, in humans, the oxidized LDL autoantibody titer has been shown to be a predictor of subsequent carotid atherosclerosis progression.[39] A direct causal link between oxidized LDL and the development of atherosclerosis, however, has not been established.

Low-density lipoproteins can be oxidized in vitro by incubation with cells derived from the arterial wall,[6,7,25,40,41] and this is a plausible means of oxidation in vivo. Susceptibility to oxidation differs among LDL preparations and is suggested to contribute to differences in LDL atherogenicity.[42-47] Lesion development may thus be a function of both levels of LDL, which is well-documented experimentally, and the tendency of these particles to undergo oxidative modification.[6] In support of a role for the latter, LDL oxidative susceptibility was recently shown to be greater in patients with angiographically proven coronary artery disease.[47] The degree to which LDL oxidative susceptibility in vitro reflects the oxidative behavior of LDL in vivo has yet to be determined. Nonetheless, much research effort is now being directed toward identifying factors, including antioxidants, that influence LDL oxidative susceptibility.

Antioxidants as Disease-Preventing Agents

Aerobic organisms are protected from the toxic effects of reactive oxygen species by a multilevel antioxidant defense network that includes agents capable of preventing or reducing oxidant generation, agents that intercept oxidants before their interaction with other biologic components, and agents that repair oxidant-induced injury.[45] Dietary micronutrients are indispensable components of the antioxidant network and include vitamin C (ascorbic acid), vitamin E (comprising tocopherols and tocotrienols, of which α-tocopherol is the predominant and most active form), and β-carotene. Vitamin C serves as a potent radical-scavenging agent in the aqueous phase, whereas vitamin E and β-carotene intercept radicals within lipid environments. The critical importance of vitamin E derives from its role as the last line of defense against oxidative injury to lipids by preventing radical chain propagation.[46]

Although not discussed in detail in this review, minerals such as selenium, copper, zinc, and manganese also function in the antioxidant network, primarily by acting as cofactors for enzymes with antioxidant activity.[48] Selenium may be particularly important in protecting the lipid environment against oxidative injury through its role as a cofactor for glutathione peroxidase, which catalyzes the reduction of lipid hydroperoxides.[48]

As evidence has accumulated in support of a role for oxidative processes in disease, attention has focused on the possible preventive properties of antioxidants. Dietary antioxidants have received particular attention in this regard because exposure to these agents varies widely among populations and can be readily manipulated by dietary changes, supplementation, or both. A preventive role for these agents is supported by several lines of evidence. Epidemiologic studies have shown a relationship between antioxidant nutriture, as indicated by food consumption patterns or direct measures of tissue concentrations of these agents, and the risk of cancer and atherosclerotic heart disease in humans.[49-59] In some cases, induced deficiencies of antioxidant micronutrients have been shown to promote,[49] while antioxidant supplementation has been shown to inhibit, carcinogenic and atherogenic processes in animals.[49,60-67] In addition, detailed

biochemical-mechanistic studies in model systems have shown that antioxidants can directly modulate relevant pathophysiologic events in vitro.[48,49,60,61,68-71] Notably missing, however, is direct evidence from randomized, placebo-controlled trials of the protective effects of antioxidants in human populations that are initially free of disease. This is considered to be the definitive test for putative antidisease agents. Several large-scale, long-term antioxidant intervention trials are currently either underway or in the planning stages[72-77] and within the coming decade are expected to expand our knowledge of the preventive properties of antioxidants.

Cancer

Dietary habits have been implicated in as much as 60% of all environmentally linked cancers, although most estimates are closer to 30%.[78] Epidemiologic studies have consistently shown that a reduced intake of fruits and vegetables, which are rich in antioxidants (Table 1),[79-81] is a major risk factor for the development of cancers of the lungs, pancreas, liver, bowel, ovaries, endometrium, cervix, and prostate.[52,53,56] Although this may partially reflect the higher fat consumption that often accompanies reduced fruit and vegetable intake,[82] evidence suggests a direct protective effect of these food groups, and this has been attributed to the presence of specific micronutrients, including vitamin C and β-carotene. Consistent with this hypothesis, indices of vitamin C and β-carotene nutriture have been shown to be inversely associated with the risk of non–hormone-dependent cancers.[51,53,57] Moreover, in cellular and organ systems and in animals, high levels of these agents have been shown to directly inhibit exposure-induced mutagenicity, malignant transformation, and tumor formation.[50,60]

Antioxidant mechanisms have been suggested to underlie the putative anticancer properties of vitamin C and β-carotene. These agents have other properties that may be important in this regard, however. Vitamin C directly suppresses carcinogen formation, enhances immunocompetence, participates in collagen synthesis, and inhibits hyaluronidase activity (which contributes to the breakdown of a mucopolysaccharide that acts as an intracellular cement).[50,51,83] The relative importance of these properties is unknown, but may vary depending on the tissue involved. β-Carotene is a precursor of vitamin A, which has well-known antitumor effects in animals, likely arising from its role in promoting cell differentiation, and could thus contribute to any observed preventive effects of β-carotene.[8,60,82] Carotenoid pigments without vitamin A activity, such as canthaxanthin and phytoene, have been shown to reduce tumor formation in animals, however, and their relative protective effects appear to correspond with their abilities to quench reactive oxygen species.[82]

In contrast to the findings for vitamin C and β-carotene, results from epidemiologic studies examining the relationship between dietary vitamin E and cancer risk have been equivocal.[84-86] Several prospective studies have noted slightly lower plasma levels of this micronutrient in persons in whom cancers subsequently developed relative to matched controls. In a recent large cohort study in Finland, for example, persons with low serum α-tocopherol concentrations had about a 1.5-fold greater risk of cancer developing, particularly gastrointestinal and uterine cancer, than those with higher levels.[54] These results are consistent with studies indicating that vitamin E inhibits exposure-induced cancers in animals.[62]

In a recently published study, disease-protective effects of antioxidant supplements were observed in a large population (>30,000 adults) in China.[87] The authors noted a substantial lowering of all-cause mortality in persons given a supplement daily for five years of the antioxidant nutrients β-carotene, vitamin E, and selenium at doses ranging from one to two times the United States recommended dietary allowance (RDA). Reduced mortality was attributed to lower rates of cancer (13%), especially of stomach cancer (21%). In contrast, no effects were observed for supplementation with retinol and zinc, riboflavin and niacin, or vitamin C and molybdenum. Although this study supports the possible benefit of specific antioxidant micronutrients as chemopreventive agents, because this study population has one of the world's highest rates of esophageal-gastric cardia cancer, together with persistently low intakes of fruits and vegetables, the applicability of these results to other populations is unclear. The effects of dietary supplementation that reduce nutrient deficiencies, which appears to have been the case in this study, may be fundamentally different from the effects of larger doses in better nourished populations.

Contrary to a chemopreventive role, recent results from the α-Tocopherol, β-Carotene Cancer Prevention Study have raised the possibility that antioxidant supplementation may actually have adverse effects in certain populations.[88] In this randomized, double-blind, placebo-controlled primary prevention trial, the effects on cancer incidence of long-term—5 to 8 years—daily supplementation with α-tocopherol (50 mg per day), β-carotene (20 mg per day), or a combination of the two were monitored in more than 29,000 Finnish male smokers.[88] No reduction in the incidence of lung cancer was observed among those receiving α-tocopherol, although there were fewer new cases of prostate cancer. Surprisingly, a higher incidence of lung cancer was noted in persons receiving β-carotene supplementation, and as a result of deaths from lung cancer and ischemic heart disease, total mortality was 8% higher. The effects of antioxidant supplementation in smokers may be different from those in nonsmoking populations. Morever, antioxidants may be most effective as preventive agents early in the disease process, and thus may be of little value after long-term smoke exposure. The epidemiologic link between lung cancer and β-carotene is among the strongest, however, and given that smokers make up the bulk of victims of lung cancer, the results are of considerable importance in terms of the limitations of antioxidant supplements and the possibility of adverse effects.

Atherosclerosis

Cross-cultural comparisons have indicated a strong inverse relationship between levels of plasma vitamin E and

heart disease mortality in humans. A significant inverse association has been found between plasma vitamin E levels in population cohorts and heart disease mortality rates among 16 European communities.[49,55] Lipid-standardized levels of plasma vitamin E and plasma vitamin E plus cholesterol were found to predict 62% and 79%, respectively, of the variance in heart disease mortality.[55] In contrast, only a modest nonsignificant association was observed for vitamins A and C. Although the results for vitamin E are intriguing, other interpopulation differences not measured may have a greater influence on disease risk.

Investigations within populations, including a number of case-control studies published over the past decade, generally have not supported an association between plasma vitamin E levels and heart disease risk. In a five-year prospective study associated with the Eastern Finland Heart Study, no difference was found in serum vitamin E concentrations between 92 victims of fatal myocardial infarction and controls matched for sex, age, smoking status, plasma cholesterol level, mean arterial pressure, and history of heart disease.[89] In the prospective Basal Study, mean cholesterol-standardized plasma vitamin E levels were not substantially lower for 67 persons who died of ischemic heart disease during the subsequent seven years than in survivors.[85] Notably, however, these studies involved measurements of antioxidants in single rather than multiple plasma specimens that had been stored long term, under conditions in which they may be unstable.

In a recently published analysis of data from more than 11,000 adults in the United States examined in the first National Health and Nutrition Examination Survey (NHANES I), a significantly reduced risk of subsequent death from all causes, particularly coronary heart disease, was observed in persons reporting a high intake of vitamin C (more than 300 to 400 mg per day).[57] A reduced risk was especially apparent in men; those in the high-intake group had an increased life expectancy of more than six years relative to those consuming less than 50 mg per day. In contrast, no evidence of a protective effect of high vitamin C intake was found in a large-scale prospective study involving more than 40,000 men and 80,000 women, but a reduced risk of coronary artery deaths was found in men and women with higher intakes of vitamin E (100 IU per day or more for two years or more).[58,59]

Although epidemiologic associations do not allow the assignment of cause and effect, some evidence for direct protective effects of antioxidants comes from animal experimentation. Induced deficiencies of vitamin C and vitamin E have been shown to result in atherosclerotic-like lesions.[49] Conversely, supplementation with these and other antioxidants has been found in some but not all cases to reduce lesion growth in hypercholesterolemic animals.[49,63-67] The extent of protection ranges from slight to pronounced, with differences likely arising from variations in animal models, antioxidant identity and dose, study duration, and atherosclerosis assessment methods. In several studies, the antiatherogenic effects of antioxidants have been shown to be greater when these agents are supplied in combination, such as vitamin E and selenium.[65]

Although vitamins C and E also produce minor beneficial alterations in plasma lipid levels, their primary protective effects are suggested to arise from their antioxidant properties. In support of this, two studies have shown protection by vitamin E even in the absence of reductions in plasma cholesterol levels.[63,64] Other effects of these nutrients also may be relevant, however. For example, differences were recently observed in the content of cell surface constituents in the endothelium of cholesterol-fed guinea pigs, depending on whether or not they also received vitamin E.[67]

Lipophilic antioxidants potentially could be particularly effective as antiatherogenic agents by virtue of their localization within the LDL particle, where they directly inhibit LDL oxidation. The oxidative resistance of LDL has been shown to be greater when vitamin E levels are increased either in vitro or through dietary vitamin E supplementation.[46,47,71,87] Whereas the addition of β-carotene in vitro has been shown to reduce LDL oxidative susceptibility,[70] β-carotene enrichment through dietary supplementation does not appear to have such effects.[90] In contrast to these antioxidants, vitamin C does not circulate within LDL, but may protect this lipoprotein by intercepting oxidants in the aqueous compartment and possibly by regenerating LDL-associated α-tocopherol (vitamin E) from the α-tocopheroxyl radical at the lipid-water interface. Although evidence of a tocopherol-sparing effect of vitamin C has been obtained for LDL in vitro,[68,69] this property has not been demonstrated in vivo.

In addition to the direct inhibition of LDL oxidation, antioxidants may reduce cellular oxidation events involved in atherosclerosis. As an example of this, cells loaded with the lipophilic antioxidant drug probucol were shown to be much less effective in bringing about the oxidative modification of LDL.[91] An elevated cellular antioxidant capacity also may reduce their sensitivity to the toxic effects of oxidized LDL.

Arguments for and Against Antioxidant Supplementation as a Disease-Preventing Measure

Given the increasing evidence of a role for oxidative processes in the development of chronic diseases and the possibility that specific antioxidants may protect against such processes, it has been suggested that increasing the intake of antioxidants through supplementation may prevent disease. Recommendations regarding micronutrient intake traditionally have been based on the concept of minimum requirements for avoiding deficiency symptoms.[79] Such constructs may be inappropriate when considering possibly protective dietary factors because levels that are adequate for preventing deficiency are not likely to provide for optimal tissue function, particularly in the presence of environmental stresses unique to modern society. As described earlier in this review, results from the

trial in Linxian, China, showed that low-dose supplementation with certain antioxidants reduced cancer mortality in an initially poorly nourished population,[87] and results of other studies raise the possibility that higher intakes of antioxidants may reduce the risk for chronic disease in the better-nourished population in the United States.[57-59] In these studies, apparently "protective" levels of vitamin C or vitamin E—5 to 10 times the RDA—exceeded those attained through normal dietary intake alone.[58-60]

Opponents of antioxidant supplementation point out that there is little direct evidence of protective effects in humans. Furthermore, although the safety of vitamin supplements that contain 100% of the RDAs is well-accepted,[92] the side effects of long-term supplementation with higher levels have not been examined prospectively.[74,75] Few serious symptoms of toxicity for these nutrients have been described (Table 1), but this may simply reflect the lack of studies addressing this issue. In a recent report, low-dose α-tocopherol supplementation was found to preserve endothelial vasodilator function in cholesterol-fed rabbits, whereas high-dose supplementation was associated with endothelial dysfunction and enhanced intimal proliferation.[93] It is possible that this dichotomy in response to low- versus high-dose antioxidants also may occur in humans. Results of the study in Finnish male smokers raise the possibility that long-term β-carotene supplementation at levels 10 to 20 times higher than in the US diet may actually be deleterious.

Apart from these arguments, most of the epidemiologic studies indicating health benefits from increased antioxidant intake are based on the assessment of dietary patterns rather than direct measures of intake of these specific micronutrients. Nutrient-based recommendations derived from food intake patterns fail to consider the importance of nutrient interactions or the possibility that other as-yet-unrecognized factors may underlie associations between dietary antioxidant intake and disease risk. Fruits and vegetables also contain appreciable levels of minerals, flavonoids, and indoles as well as carotenoids other than β-carotene, and these or other agents may have protective properties.[52]

Indeed, before definitive recommendations can be made regarding the prophylactic use of antioxidants, the following questions need to be addressed in humans:

- Do antioxidant vitamins actually prevent or reduce the development of chronic diseases? If so, which antioxidants are most effective in preventing disease and at what doses?
- How do the possible benefits and optimal doses vary in relation to the nature and stage of the disease?
- Do antioxidants have a role in secondary prevention?
- Are there interactions among antioxidants or between antioxidants and other dietary factors, such as fat composition, that influence their effectiveness?
- How do genetic and environmental factors—cigarette smoke exposure, for example—influence antioxidant nutriture or effectiveness in preventing disease?
- Are toxic effects of long-term antioxidant supplementation observed at doses required for disease prevention?

A number of prospective trials addressing some of these questions in US populations are currently underway.[74-77] Among these are the following:

- The Physicians' Health Trial, a study involving 22,000 men taking either β-carotene or a placebo, which is scheduled for completion in 1996;
- The Women's Health Study, an investigation of the preventive effects of β-carotene, vitamin E, and aspirin in women older than 50 years, which was begun in 1992; and
- The Carotene and Retinoid Efficacy Trial (CARET), a study examining the ability of β-carotene plus retinyl palmitate to reduce lung cancer incidence in 18,000 men and women who are either smokers or who

TABLE 1.—*Natural Sources, Physiologically Relevant Doses, and Side Effects of Antioxidants in Humans*

Antioxidant	*Dietary Sources*	*Recommended Dietary Allowance**	*Toxicity Level†*	*Reported Side Effects at High Doses†*	*Contraindications†*
Vitamin C	Fruits (particularly citrus), green leafy vegetables, tomatoes, potatoes	Nonsmokers: 60 mg/day Smokers: 100 mg/day	Adverse effects observed at doses of ≥1 gram/day	Urinary oxalate excretion, kidney stone formation, increased iron absorption, gastrointestinal disorders	Renal insufficiency, iron overload
Vitamin E	Vegetable oils, whole grains, nuts and seeds, green leafy vegetables	Men: 15 IU/day Women: 12 IU/day	No consistent adverse effects with doses up to 3,000 IU/day for months	Fatigue and weakness, gastrointestinal disorders, breast soreness (women), bleeding	Subjects receiving vitamin K antagonists as anticoagulants
β-Carotene	Green leafy vegetables, yellow-orange fruits, and vegetables	None established‡	Appears to be nontoxic even when taken in large doses over years	Carotenodermia (presumed innocuous)	

*Values are for adults (≥19 years of age); taken from the National Research Council.[79]
†From the National Research Council,[79] Sestili,[80] and Bendich and Machlin.[81]
‡The typical United States diet contains 1 to 2 mg/day, or 1,700 to 3,500 IU/day.

have a history of asbestos exposure.

Based on current knowledge and regard for scientific data as a basis for clinical decision making, advocating proper food selection with a high intake of fruits and vegetables should be the primary message of the health care community in response to the growing interest in antioxidants. This approach avoids the possibility of toxic side effects from supplements and emphasizes the role of the total diet in determining disease risk.[75] As few as 10% of Americans are estimated to consume five servings of fruits and vegetables per day.[56,94] Thus, there is much room for beneficial changes in the eating habits of the US population.

Populations With Increased Antioxidant Needs

Special consideration should be given to persons likely to be at increased risk of inadequate antioxidant intakes due to genetic or environmental factors that may increase antioxidant requirements. Although still relatively unexplored, several specific factors affecting individual antioxidant requirements have been identified. The best-known example is cigarette smoke, which contains numerous oxidants and appears to increase endogenous oxidant production.[95-99] Severe depletions of circulating antioxidants, presumably indicative of reduced body stores, are a measurable effect of the oxidant burden imposed by cigarette smoke. Reductions in plasma vitamin C levels as great as 75% have been reported in smokers compared with nonsmokers, depending on age, sex, and smoking history.[100-105] Although reduced vitamin C consumption and bioavailability are possible contributors,[106,107] increased vitamin C turnover is largely responsible for the poor vitamin C status of smokers.[108] Reductions in lipophilic antioxidants also have been reported, with results being more consistent for β-carotene than for vitamin E.[109-112]

Recognizing the increased vitamin C requirements of smokers, the National Research Council recently increased the RDA from 60 to 100 mg per day for this subpopulation.[92] Several studies, however, have suggested that even this may not be enough.[103-105] We recently observed that plasma vitamin C concentrations were lower in heavy smokers (≥ 1 pack per day) reporting daily intakes of vitamin C greater than 250 mg as compared with nonsmokers reporting similarly high intakes. In the same study, we also observed lower plasma vitamin C levels in nonsmokers with regular exposure to environmental tobacco smoke than in nonsmokers without such exposure, even at dietary vitamin C intakes above the RDA for smokers. Thus, it appears likely that such intakes may not be adequate to maintain needed body stores in nonsmokers with exposure to tobacco smoke.[105]

The increased antioxidant requirements and risk of disease associated with exposure to tobacco smoke and other environmental agents,[77,113-115] including ultraviolet irradiation and certain food constituents such as nitrosamines, may justify recommendations for low-dose supplementation in persons with such exposure. Caution is recommended, however, because recent results have suggested that higher dose supplementation, particularly with β-carotene, may be deleterious in long-term smokers.[88] Any recommendations for antioxidant supplementation should be coupled with recommendations for reducing exposures—smoking cessation, for example.

Conclusion

The compelling evidence of a role for oxidative processes in a variety of chronic diseases is likely to lead to increased research attention to the preventive properties of antioxidants, and the results of such studies may affect approaches for preventing and treating chronic diseases. Current evidence supports recommendations for diets containing food groups that are naturally high in antioxidants. Recommendations for increasing antioxidant intake through supplementation cannot be made on the basis of current scientific evidence, however, because to date most of the data supporting a protective effect in humans are epidemiologic, and some evidence of side effects has been presented. Nonetheless, because of the widespread availability of antioxidant supplements and the mass media's promotion of their consumption, many patients will make an independent decision to supplement. Physicians may choose not to discourage such practices, particularly in high-risk patients, but may wish to provide counsel regarding the preliminary nature of scientific data supporting the benefits and evidence of possible side effects of antioxidant supplementation (see the Page for Patients at the end of this article).

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Do Antioxidants Combat Disease?

A Page for Patients From The Western Journal of Medicine and Your Physician

Why should anyone care about oxidants?

Scientists now think that oxidants may contribute to the two biggest killers in the United States—cancer and heart disease.

What are oxidants?

Oxidants are reactive molecules that bring about chemical changes in other molecules. Some oxidants are free radicals, which are particularly reactive because they have unpaired electrons. As a result, they are unstable. But they can become stable by robbing electrons from other molecules. This breaks important chemical bonds in the robbed molecules, which then become unstable. The cycle continues as the robbed molecules then react with other molecules in a chain reaction.

How can oxidation promote cancer?

Oxidation—robbing a molecule of electrons—can cause a change in the molecule's structure. If that robbed molecule happens to be DNA, the blueprint for every molecule in your body, this can cause mutations, which may lead to cancer.

How can oxidation promote heart disease?

Like DNA, low-density lipoproteins (LDL, the so-called bad cholesterol) can become oxidized. Scientists now think that oxidized LDL makes the fatty plaque in arterial walls bigger and narrows blood vessels. Narrowed blood vessels in the heart (or "coronary artery disease") can cause heart attacks because the heart muscle cannot get enough of the blood it needs to function properly.

How can I protect myself against the damaging effects of oxidants?

The body depends on an extensive network of compounds known as antioxidants to do just that. Antioxidants are generous molecules: they donate their own electrons to oxidants so that the oxidants won't rob other molecules (like DNA). Vitamins such as C and E, β-carotene, and minerals such as selenium, zinc, and manganese all participate in the antioxidant network. But they also may play other roles in your body. For example, vitamin C helps keep the substances between your cells intact.

How can I improve my body's antioxidant capacity?

The body makes some of its own antioxidants, but gets a large supply from the foods we eat. Dark green, leafy vegetables—like spinach or kale, but not the pale leaves you find in iceberg lettuce—are especially good sources of antioxidants because they have vitamin C, vitamin E, and β-carotene. Vitamin C can be found in high amounts in citrus fruits, but other fruits, tomatoes, and even potatoes also have vitamin C. β-Carotene is present in yellow-orange fruits like cantaloupe and vegetables like squash and carrots. Large amounts of vitamin E can be found in vegetable oils, whole grains, nuts, and seeds.

In addition to eating foods enriched in antioxidants, it is also important to protect yourself against factors that can deplete antioxidants, such as exposure to cigarette smoke or infection.

Why is it good to get antioxidants from the foods I eat? Why not just take a vitamin supplement?

Different antioxidants work in slightly different ways and in different parts of your body, and they all work together to form a network of protection. If one antioxidant is limited, it may limit the entire system. To ensure that you get the proper complement of antioxidants, eat a well-balanced diet rich in fruits, vegetables, and whole grains.

Can vitamin supplements containing antioxidants be bad for me?

Some vitamins and minerals, if taken in high doses, can be dangerous, like any medication. But it is practically impossible to eat enough fruits and vegetables to get an overdose of antioxidants or other important vitamins and minerals that are found in these foods. So eating a variety of fruits and vegetables—which are also naturally low in fat, high in fiber, and cholesterol-free—is the smartest way to get your antioxidants.

Editorials

Do Guns Matter?

In this issue of The Western Journal of Medicine, Jeffrey Kahn, a medical student, presents data on the public health effects of firearm violence in California. His analysis is followed by four policy recommendations. These include repealing California's preemption law, creating a state advisory body, increasing liability for unsafe storage or transfer of firearms, and registering all firearms and firearm owners in the state.[1]

Each of these strategies represents an attempt to reduce firearm violence by restricting access to guns or modifying specific aspects of their design, or both. The wisdom of this approach rests, in turn, on the fundamental assumption that the gun matters. Not everyone agrees. The opposing viewpoint is summarized by a famous National Rifle Association slogan—"Guns don't kill people; people kill people."

Few dispute the fact that firearms are highly effective weapons. The case-fatality rate for assaults with a gun (the fraction that end in death) is two to five times higher than the case-fatality rate for assaults with a knife.[2] Self-inflicted lacerations account for 15% of nonfatal suicide attempts in the United States, but only 1% of suicides.[3] Firearms, on the other hand, are rarely implicated in nonfatal suicide attempts, but three fifths of all completed suicides in the United States involve firearms.[3]

Two competing explanations can be offered for these facts. The first is that firearms make killing easier. Guns give persons the power to inflict lethal force with relatively little effort. Because, on average, a gunshot causes more damage than a comparable wound inflicted by a knife, victims of gun attacks die of their injuries more often than victims of knife attacks.[4] Advocates of gun control believe that if guns were less readily available, fewer serious injuries would result and fewer victims would die.[5]

Opponents of gun control reject this assertion. They maintain that choosing a gun to commit homicide simply reflects the strength of the assailant's intent to kill.[6] According to this view, would-be murderers not only seek out firearms, but they aim more carefully and try harder to kill their victims than criminals who use less dangerous weapons.[4] If this is true, strategies to reduce the availability of guns will not succeed because would-be killers will either work harder to acquire a gun or kill by other means.[7]

Although it is impossible to measure intent directly, it is evident that many criminals use guns without a premeditated plan to kill. Wright and colleagues surveyed a large convenience sample of incarcerated felons about their reasons for carrying a gun. Most reported that they used guns to forestall or overcome victim resistance and to escape unharmed. The most commonly cited reason was "Don't have to hurt victim." More than three fourths of the criminals who actually fired their guns claimed that they had no previous intent to do so.[8]

Because convicted felons may be less than truthful, their statements must be taken with some skepticism. Studies show, however, that robbers who use guns are more successful at completing their crimes and less likely to injure their victims than robbers who use other weapons.[2,4,5] Unfortunately, we can take little solace from these facts. Although the overall rate of injury in firearm robberies is less than the rate of injury in robberies without a gun, the proportion of gun robberies that result in the death of the victim is three times larger than that for knife robberies and ten times the rate for robberies with other weapons.[9]

Robbery accounts for a relatively small percentage of intentional injuries. Most occur as the result of arguments or altercations between friends, acquaintances, or family members. Zimring studied a large series of aggravated assault cases in Chicago and found that most were precipitated by alcohol and anger instead of a premeditated intent to harm. In more than 80% of gun and knife attacks, only a single wound was inflicted. This suggests that many assailants were more interested in disabling than killing because they did not inflict additional wounds to ensure the death of the victim. Nonetheless, victims who were shot were five times more likely to die than victims who were stabbed.[10]

In another study, Zimring found that the type of gun involved in a firearm assault also influences outcome. The fatality rate among victims shot by large-caliber handguns was substantially higher than the fatality rate among victims shot by small-caliber handguns.[11] Although one cannot exclude the possibility that offenders intent on killing went to special lengths to secure large-caliber handguns before these assaults, the location of wounds and other factors suggest otherwise. In a fight, combatants tend to reach for the most readily available weapon. The more lethal the weapon, the more likely death will occur.[2,4,5]

Ironically, the qualities that enhance the lethality of firearms (such as magazine capacity, rate of fire, and "stopping power") are precisely the qualities that make them most desirable as weapons for self-defense. Keeping a gun in the home for protection, however, may do more harm than good.[12] This is particularly true in homes with children and in households marked by alcoholism, drug use, depression, or family violence.

One study of family and intimate assaults in Atlanta, Georgia, revealed that attacks with a gun were 12 times more likely to end in death than attacks by other means.[13] An analysis of 12 years of homicide statistics from the Federal Bureau of Investigation determined that twice as many women were murdered with a gun by their husbands or intimate acquaintances than were killed by strangers using a gun, a knife, or any other means.[14] When a woman killed with a gun, the victim was five times more likely to be her spouse, an intimate acquaintance, or a family member than to be a stranger or a victim of undetermined relationship.[14]

The results of a recent case-controlled study suggest that homes where guns are kept are almost three times more likely to be the scene of a homicide than comparable homes without guns, even after the independent effects of victim age, sex, race, neighborhood, previous family violence, anyone using illicit drugs, and any history of previous arrests were taken into consideration.[15] A gun in the home did not afford protection from homicide by an intruder. Instead, guns were linked to a markedly increased risk of homicide at the hands of a spouse, a family member, or an intimate acquaintance.[15]

Does this mean that guns are inherently bad? Of course not. Two things must be present for gun violence to occur—violence and immediate access to a gun. In the absence of violence, a gun is no more dangerous than a bucket of gasoline. A lighted match can certainly start a fire, but the potential for serious injury or death is much greater if you toss in a bucket of gasoline. Likewise, violence can certainly cause harm, but the potential for serious injury or death is increased when a firearm is involved.

The question is this: How can we keep the two apart as often as possible? To paraphrase Sam Levinson, it is not hard to be brilliant. All you have to do is think of something stupid and do the opposite.[16] It's stupid to encourage people to keep guns in their homes for protection without a clear understanding of the overall balance of benefits and risks. It's stupid to let people who have committed a violent crime legally purchase guns because they were smart enough to plea-bargain their charge to a misdemeanor. It's stupid to ignore private sales and theft, which are the major sources of supply to the criminal market.[2,17] And it's stupid to permit firearms to be manufactured in the United States without any regard for safety, quality, or capacity for harm.[18]

Physicians are playing an increasingly important role in this debate. Organizations such as the American Public Health Association, the American Academy of Pediatrics, the American College of Surgeons, and the American College of Emergency Physicians have adopted strong position statements in support of efforts to curb firearm violence. To assume that gun control alone will cure our epidemic of violence would be naive. On the other hand, it would be equally naive to ignore the fact that firearms magnify the consequences of interpersonal violence.

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Ocular Infections—A Rational Approach to Antibiotic Therapy

UNTIL THIS CENTURY blindness was frequently the result of serious ocular infection. Before 1900 an estimated 20% to 79% of children in institutions for the blind in Europe were there because of gonorrheal ophthalmia at birth.[1] In the first half of the 20th century, the incidence of serious eye infections declined because of general improvements in health and nutrition and because of simple public health measures such as Credé's prophylaxis: 1% silver nitrate instilled into both eyes at birth. With the introduction of antibiotics in the 1940s, effective treatment of blinding ocular infections finally became a reality. Since that time, to echo a popular slogan, "We've come a long way."

In the review article elsewhere in this issue of the journal, Robert W. Snyder, MD, PhD, and David B. Glasser, MD, discuss in detail the current concepts of antibiotic therapy for ocular infections and the treatment regimen for some of the more common serious eye infections.[2] At first glance the most striking observation in the article is the wide choice of antibiotics available to clinicians today. Despite the emergence of new strains of bacteria that are more and more resistant to the antibiotics currently available,[3] there always seems to be a new "technologic fix" on the horizon that promises to keep us ahead of the game. The current "fix" in ophthalmology is a new class of antimicrobial agents, the fluoroquinolones. These agents initially held great promise as broad-spectrum antibiotics that could be used as monotherapy for the treatment of severe bacterial keratitis.[4] The emergence of resistant strains of bacteria, especially streptococcal species, however, has called into question the use of these

TABLE 1.—*Classes of Antibacterial Agents**

Penicillins	Tetracyclines
Cephalosporins	Chloramphenicol
β-Lactamase inhibitors	Lincosomides
Carbapenems	Aminoglycosides
Monobactams	Aminocyclitols
Macrolides	Metronidazole
Glycopeptides	Sulfonamides
Rifamycins	Trimethoprim
Peptolide	Fluoroquinolones

*From Jones.[6]

agents as the sole treatment of severe corneal infections.[5] But there are more antibiotics to choose from. In a recent review of the literature, 18 classes (Table 1) of antibacterial agents available for the treatment of infectious eye diseases were listed.[6] Third-generation cephalosporins like ceftazidime, β-lactamase inhibitors such as the combination of ticarcillin and clavulanic acid, and newer macrolides including clarithromycin and azithromycin have all filled important niches in the treatment of ocular infectious diseases. A glycopeptide, vancomycin, has assumed the primary therapeutic role in treating infections caused by methicillin-resistant staphylococci and streptococci. Resistance to vancomycin is rare. A new glycopeptide antibiotic, teicoplanin, has similar properties but has less vestibular toxicity and ototoxicity.[7]

Despite a veritable cornucopia of antibiotic agents, new strains of resistant bacteria continue to emerge at an alarming rate. Even more disturbing is the likelihood that fewer new antibiotics will be introduced in the next decade than in previous years because of the excessive cost involved in developing a new chemical product. It is likely that many more fluoroquinolones will be introduced and that they will have improved antibacterial activity, but in general, developments will focus on drug delivery and bioavailability.[8] Genetic engineering holds great promise for future rational drug design to tailor antibiotics to special needs. An example is the lantibiotics, a class of antimicrobial peptides that are synthesized by posttranslational modification. The range of biologic effects exhibited by lantibiotics is extraordinarily diverse and appears to be the consequence of several different mechanisms. An enormous variety of ribosomally synthesized and posttranslationally modified antimicrobial substances is possible, and these agents may prove to be the antibiotics of the future.[9]

Paradoxically, the current availability of so many excellent antibiotics has in some cases adversely affected the diagnosis and treatment of ocular infections. The management of severe ocular infections has traditionally depended on a rational stepwise diagnostic approach that included carefully taken specimens for culture, subsequent antibiotic sensitivity testing, and specific antibiotic therapy based on an etiologic diagnosis. Broad-spectrum antibiotic therapy, better known as "shotgun" therapy, was used only in the early course of an infection before a specific bacterial pathogen was identified. But with the increasing availability of effective broad-spectrum antimicrobial agents, the trend has been to forego the rational diagnostic approach and to depend on these new "superdrugs," either singly or in combination. A reliance on empirical treatment has also been driven by increasing concern about the cost-effectiveness of diagnostic procedures, specifically cultures and sensitivity tests.

In a recent survey evaluating community care of patients with corneal ulcers, antibiotic therapy was instituted without cultures being obtained in 48.7% of all cases being observed by general ophthalmologists. Of interest is that the figure for a tertiary care corneal and external disease service evaluating the same problem was 48.1%.[10] Compliance with standard recommended practice in the care of corneal ulcers appears to be poor, in this instance even by corneal specialists.

Antibiotic sensitivity testing has also been a mainstay of the rational approach to managing severe ocular infections. Admittedly, conventional laboratory tests using antibiotic disk diffusion on agar plates inoculated with the bacterial pathogen are crude in comparison with more sophisticated methods using in vitro broth dilution assays that test minimal inhibitory concentrations.[11] Other methods are being developed at present, however, that promise to revolutionize the concept of antibiotic sensitivity testing. With newer decimal assays, combinations of antibiotic drugs can be evaluated to determine whether there is an additive, synergistic, or antagonistic effect on the bacterial pathogen in question.[12] Highly accurate quantitation of the additive effects of two or more antibiotics on a specific pathogen will undoubtedly provide extremely useful information for clinicians who are caring for patients with severe ocular infections.

Empiric treatment of severe ocular infection without the benefit of cultures and sensitivities is fraught with unnecessary risk. Even if empiric broad-spectrum antibiotic treatment is effective in eradicating a pathogen, the toxic effects of the drug on the cornea or the retina may result in blindness. In the case of bacterial endophthalmitis, empiric broad-spectrum intravitreal therapy is always indicated at the time of diagnostic aqueous and vitreous aspiration, but because of the potential for retinal toxicity, some antibiotics should be avoided.[13] Aminoglycosides are especially damaging to the retina, producing macular infarction even while the infection is successfully responding to treatment. Mounting evidence suggests that aminoglycosides, including amikacin, have a threshold for retinal toxicity that is dangerously close to the therapeutic drug level. It also appears that ceftazidime has a much broader and safer dose range and that it is as effective as aminoglycosides for the treatment of ocular gram-negative infections.[14]

Snyder and Glasser have provided an excellent overview of antibiotic therapy for some of the more serious and refractory ocular infections seen by ophthalmologists. Their article is comprehensive and represents the standard of care for the rational approach to antibiotic

therapy. In this era of cost-benefit analysis, outcome studies, and practice guidelines, I applaud their concern for quality of care above all other considerations. In the treatment of severe ocular infections, the rational approach ultimately ensures both quality of care and cost-effectiveness. The price of failure is blindness. The measure of success is the gift of sight.

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Correspondence

Medical Practice Guidelines

To the Editor: The article on medical practice guidelines by Walker and colleagues was interesting and unbiased.[1] We agree that the adverse consequences of practice guidelines have not been fully assessed. We would like to comment on the negative effects of such guidelines.

Practice guidelines cannot keep up with the pace of clinical research. Most guidelines still rely heavily on expert opinion rather than on evidence. Expert opinion is frequently biased, outdated, and often contrary to the evidence.[2] For example, in the recent guidelines on early human immunodeficiency virus infection, only 8% of the recommendations were supported by evidence.[3] Clinical medicine in practice is frequently controversial, and guidelines issued by a panel of experts may be contrary to what other experts on the same subject think. For instance, the guidelines on the use of prostate specific antigen as a screening test for prostate cancer, issued by six different expert groups, are contradictory.[4]

Clinical epidemiologists have pointed out that the best way to keep up to date is by critically reviewing original research articles.[5] Computerized databases like MEDLINE or PDQ provide instant access to this information. It is easy to compile and critically review pertinent literature when needed. Practice guidelines make it difficult for residents and students to learn critical appraisal of the literature. Like original research articles, guidelines should be read with a certain degree of skepticism.

We therefore discourage the use of practice guidelines by clinicians interested in critically appraising published research.

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The Authors Respond

To the Editor: Drs Rajkumar and Sampathkumar make a number of perceptive observations in extending our discussion of the potentially deleterious consequences of medical practice guidelines. Their chief criticism—that guidelines do not keep pace with current research—does not, in itself, negate the importance of guidelines. Guidelines have proliferated precisely because the scope and pace of clinical research have made it nearly impossible for practitioners to stay current in more than a few practice areas. Unfortunately, clinicians generally do not have the time or resources necessary to personally review the relevant scientific literature every time they encounter a problematic clinical circumstance. Moreover, recent empirical reports, which themselves often yield contradictory findings, are generally reviewed by only a handful of persons and must be integrated with what is already known in a field. Although "expert opinion" can, particularly in poorly researched areas or in areas of emergent importance such as the acquired immunodeficiency syndrome, lead to contradictory treatment prescriptions,[1] it is generally to be preferred over recommendations based on a smaller number of less well-established physicians. Most proponents acknowledge that guidelines should be updated regularly in response to relevant scientific developments, although the optimal frequency of guidelines review activities needs to be established for individual practice areas.

More than 1,500 formal guidelines have been published, and guidelines development has been described as a growth industry for the 1990s. Thus, it is unlikely that practitioners will be able to remain up to date with guidelines that are pertinent to their practices, let alone the published studies on which they are based. A well-recognized, though poorly addressed, problem currently confronting physicians is how to manage the exponential growth of scientific knowledge in a manner that best informs their practice. Guidelines are the principal modern solution to the explosive growth of medical research, but their effects and potential role in malpractice litigation have not been sufficiently examined. They are not panaceas and should be critically evaluated, as Drs Rajkumar and Sampathkumar rightly observe.

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The FDA and Terfenadine

To the Editor: In the article by Zechnich and co-workers on interactions between the antihistamines terfenadine and astemizole and other agents, the authors conclude that "informing physicians may have limited efficacy in preventing episodes of concurrent use" of terfenadine or astemizole and macrolides or antifungal azoles.[1(p324)] We agree with them that educational efforts do not necessarily result in improved performance by the targeted population. For example, intensive measures such as special programs, the use of videotapes, and in-service sessions have failed to increase the compliance of health care workers with infection control practices.[2-4] This behavior is inexplicable; unlike potential drug reactions, these practices consistently decrease the incidence of hospital-acquired infections.

This phenomenon, however, is not limited to physicians or nurses. In their study, Zechnich and colleagues showed that the same pharmacy was involved in 97% of concurrent-use episodes. Pharmacists continued to dispense medications with potentially hazardous side effects despite interventions by pharmaceutical companies—at least after the earlier warning letters—targeting not only physicians but also pharmacists.

We agree with the authors that their study period does not permit the measurement of the full effect of governmental and industrial warning campaigns. But because the best outcome is usually seen soon after an intervention, we examined the effect that the July 1992 US Food and Drug Administration (FDA) public warning may have had on terfenadine use. We extrapolated the maximum number of terfenadine tablets prescribed during June, August, and September of 1991 and 1992 from Figure 1 in their report.[1(p322)] By comparing terfenadine use during and after the allergy season in both years, we found that the FDA's press release had a significant effect on the number of prescriptions (χ^2, $P<.0001$). Although there was a trend toward significance for the relationship between the FDA release and estimates of concurrent-use episodes during the months of June and September of both years (Figure 2),[1(p323)] no conclusions could be drawn. The number of episodes is small and is a function of prescribed terfenadine.

We conclude that the FDA's public warning had an effect on dispensing terfenadine and possibly on the concurrent prescribing of other drugs. Although we do not know who was ultimately responsible for the reduction in terfenadine use—physicians or pharmacists—we suspect it was both.

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* * *

Drs Zechnich and Haxby Respond

To the Editor: The comments submitted by Dr Hakim and Ms Stahl are appreciated. In particular, they provide references to other published reports that document the limited effect of some educational programs in changing the practice behavior of health care professionals. There may be many reasons for this limited effect. In the case of prescribing possibly interacting medications, we hypothesize that prescribers may have limited information regarding a patient's full medication profile. In 48% of the episodes of concurrent prescribing in our report, patients received the two medications from different physicians. Even if these prescribers were aware of the possible interaction, access to the full medication profile may be limited in many cases, and thus, educational efforts for physicians alone also may be limited. Informing pharmacists is a key component of any such educational efforts.

We have serious concerns regarding these authors' analysis of the data published in the original report. According to their analysis, the number of terfenadine prescriptions before and after the allergy season varied between 1991 and 1992 to a degree unlikely to be caused by chance alone. The conclusion that this difference must be because of the US Food and Drug Administration (FDA) press release without controlling for significant confounding effects is unfounded, however. As discussed in the original report, because of the natural lag between dispensing medication and submitting a claim to Medicaid, we cannot assume that data are complete from August and September 1992. Natural variation from year to year or within a given allergy season may be substantial and may affect the volume of antihistamines prescribed. We suspect that many prescribers may have switched patients to astemizole therapy, further reducing terfenadine prescribing without reducing potential risk. Finally, prescribers may have become aware of these interactions from sources other than the FDA press release. When the Drug Use Review of Oregon notified the physicians and pharmacists who were identified in our investigation about the concurrent prescribing, we surveyed these health care workers. Of responding physicians, 42% reported that they learned about this interaction from the manufacturer's letter and 12% as a result of the press release. In short, the presence of these confounding variables limits the ability to draw reliable conclusions. Furthermore, such analysis must focus on the extent of concurrent prescribing, rather than the number of terfenadine prescriptions. In fact, their analysis of concurrent prescribing failed to show a statistical difference.

While we believe that efforts such as the FDA press release are essential and probably do have considerable effect, the limited data in our investigation cannot support this conclusion. Perhaps a well-controlled time-series analysis would more accurately assess this issue, and we are currently pursuing such an evaluation. While researchers continue to try to identify the best way to prevent interactions, such widespread efforts to inform health care professionals should be strongly encouraged.

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Oregon Health Plan—Clarification

To the Editor: I found the Special Series in the July issue on health care reform to be interesting and informative. As one of the original Commission members who formulated the Oregon Health plan,[1] I was particularly interested in the article by Dr Young.[2] I do have one small correction to his comment on page 75, "Services below this line were not to be available." This is commonly stated, but it would be more accurate to say, "Services below this line were not to be paid for." Oregonians desiring low-priority procedures that the state legislature has decided not to fund may still be able to receive them—and definitely will be able to receive a diagnosis—but the physicians and hospitals who provide these services will not be compensated for them. The hope is that this will cause Oregonians to think about where they want to spend their limited health care dollars and reward preventive and more efficacious treatment.

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* * *

Dr Young Responds

To the Editor: I am grateful to Dr Allen for clarifying this point. I meant to say that services below this line were not to be available through the State's Medicaid program. Dr Allen's hope that "this will encourage Oregonians to think about where they want to spend their limited health care dollars, and reward preventive and more efficacious treatment" is one that is shared by all of us concerned about meaningful rather than politically expedient health care reform.

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Physicians and Health Care Reform

To the Editor: The article on physicians' attitudes towards health care reform[1] was seriously flawed by what the authors describe as a "limitation"—the only choices they presented were managed competition, a single-payer system, or no change. Their justification, that these are the plans "that are currently receiving the most serious consideration nationally," simply will not do for two reasons: it is not true and what is being considered by nonphysicians should have little bearing on deciding what physicians think is best.

It is not true because the Republican bill also has a great many supporters both in and out of Congress. It is true that it is not being considered for the next few months because the Democratic leadership in the Congress will not let it be considered there, but virtually all political observers I have heard or read lately agree that both options above will have no chance after the coming elections.

What is being considered by nonphysicians is barely relevant to what physicians think is best. For example, a patient has pneumonia, and we are offered the choice of treating him with tetracycline, aspirin, or fluconazole. Most of us would not fall for this; we would ask, "Where is the penicillin?" Similarly, we have a sick health care system caused by government interference in the physician-patient relationship and government-stimulated insurance interference in that relationship—including the antitrust stance of the government against physicians. The choices that Malter and colleagues offer us for treating the health care system are much more government and insurance company interference, nearly complete government interference in the relationship, or leave it as sick as it is. This is nonsense. We need a choice of how to get the government and insurance companies back where they belong—as advisors to patients and reimbursers of charges that they cover. The American Medical Association and Republican plans both have many aspects favorable to this goal, and a real survey should include them.

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* * *

The Authors Respond

To the Editor: Dr Hamilton is correct to note that our survey did not assess the attitudes of physicians about all types of proposed health care reform. As we discussed in the article, we focused on managed competition and single-payer reforms for two reasons. At the time of the survey these were the proposals being considered most seriously nationally. Also, these were the only two plans—and indeed still are the only two plans—that would provide universal coverage.

Providing universal coverage has been one of the principal goals driving health care reform. This is a goal not only of the public and many of our political leaders, but also of numerous physician groups, including the American Medical Association. Unfortunately, most experts agree that plans that rely on incremental reforms such as those calling for increased insurance regulation, increased use of medical savings accounts, or the use of individual mandates to require persons to buy their own insurance will not substantially increase coverage.

Dr Hamilton is correct: some physicians and physician groups do advocate incremental or minimal change. In our survey 20% of physicians favored incremental changes while 80% favored "fundamental" changes or greater. Of course, groups that advocate incremental or minimal change may have a valid position. They should acknowledge, however, that their proposals are unlikely to improve access for the uninsured and to curb the rising cost of health care.

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Using the Fax—Concerns About Patient Confidentiality

To The Editor: We are writing in response to Dr Bowie's letter, "Using the Fax,"[1] Although he makes a good argument for the advantages of facsimile (fax) technology as a means of rapid transmission for medical records, we are concerned about the potential consequences of faxing medical documents, which may threaten patient confidentiality.

In a recent letter to the editor,[2] we illustrated our concerns using two cases in which errors in fax transmission resulted in notable breaches of patient confidentiality. We suggested adoping five safeguards intended to minimize the chance of such errors while allowing the continued use of this valuable technology. The recommendations were as follows:

- Educate medical and support personnel about the concerns regarding fax errors;
- Encourage personnel to take responsibility for confirming accurate reading and entry of destination numbers;
- Notify the recipient by telephone of the intent to transmit a fax before sending confidential information;
- Address the cover sheet to a person rather than an institution or organization and include a legal notice regarding the confidential nature of the subsequent page(s); and
- Select carefully those records that need to be faxed versus those that could be sent via more traditional means. Some information is inappropriate for faxing except under extreme circumstances. In those cases, patients should be included in decisions regarding the mechanism of transfer of their own medical records.

We support the development of technologies that facilitate rapid communication within the medical profession. We urge caution, however, when sending confidential information by facsimile.

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

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Medical Staff Coordinator
Sunnyvale Medical Clinic
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(408) 730-4309

Sunnyvale Medical Clinic

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Bruce Manziello, MD, FACP
Chief of Staff
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MARCH 5-10: COPING WITH CURRENT ISSUES IN CLINICAL PRACTICE featuring Drs. Paul Appelbaum, Charles Nemeroff, Glen Gabbard, Walter Menninger, and Bernard Beitman. Location: Park City, UT. Cost: $395 through February 4 (daily rates are available). CE Credit: 28 hours. Contact: The Menninger Clinic, Continuing Education (800) 288-7377.

PEDIATRICS–1995 ANNUAL MEETINGS. The American Pediatric Society, the Society for Pediatric Research, and the Ambulatory Pediatric Association, May 8-11, 1995, San Diego Convention Center, San Diego, California. Contact: APS/SPR Association Headquarters, 141 Northwest Point Blvd, PO Box 675, Elk Grove Village, IL 60009-0675. Call (708) 427-0205; FAX (708) 427-1305. Or: Ambulatory Pediatric Association, 6728 Old McLean Village, McLean, VA 22101. Call (703) 556-9222; FAX (703) 556-8729.

Eleventh Annual Cardiovascular Conference at Lake Louise. March 6-9, 1995. Lake Louise, Alberta, Canada. Fees: $410 for ACC members; $495 for non-members; $250 for fellows-in-training, residents, physician assistants, nurses, and technologists. For information, call:

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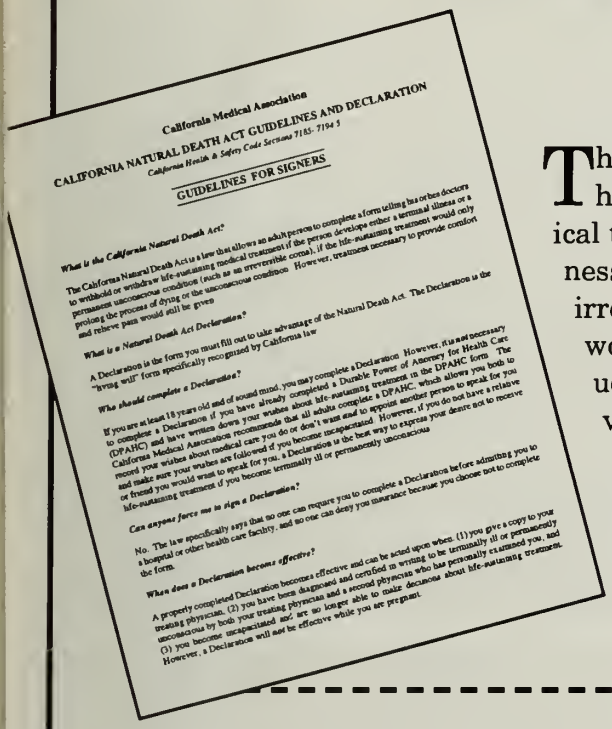
California Medical Association

California Natural Death Act Guidelines and Declaration Order Form



California Medical Association

CALIFORNIA NATURAL DEATH ACT GUIDELINES AND DECLARATION

California Health & Safety Code Sections 7185-7194.5

GUIDELINES FOR SIGNERS

What is the California Natural Death Act?

The California Natural Death Act is a law that allows an adult person to complete a form telling his or her doctors to withhold or withdraw life-sustaining medical treatment if the person develops either a terminal illness or a permanent unconscious condition (such as an irreversible coma), if the life-sustaining treatment would only prolong the process of dying or the unconscious condition. However, treatment necessary to provide comfort and relieve pain would still be given.

What is a Natural Death Act Declaration?

A Declaration is the form you must fill out to take advantage of the Natural Death Act. The Declaration is the "living will" form specifically recognized by California law.

Who should complete a Declaration?

If you are at least 18 years old and of sound mind, you may complete a Declaration. However, it is not necessary to complete a Declaration if you have already completed a Durable Power of Attorney for Health Care (DPAHC) and have written down your wishes about life-sustaining treatment in the DPAHC form. The California Medical Association recommends that all adults complete a DPAHC, which allows you both to record your wishes about medical care you do or don't want and to appoint another person to speak for you and make sure your wishes are followed if you become incapacitated. However, if you do not have a relative or friend you would want to speak for you, a Declaration is the best way to express your desire not to receive life-sustaining treatment if you become terminally ill or permanently unconscious.

Can anyone force me to sign a Declaration?

No. The law specifically says that no one can require you to complete a Declaration before admitting you to a hospital or other health care facility, and no one can deny you insurance because you choose not to complete the form.

When does a Declaration become effective?

A properly completed Declaration becomes effective and can be acted upon when: (1) you give a copy to your treating physician, (2) you have been diagnosed and certified in writing to be terminally ill or permanently unconscious by both your treating physician and a second physician who has personally examined you, and (3) you become incapacitated and are no longer able to make decisions about life-sustaining treatment. However, a Declaration will not be effective while you are pregnant.

This directive allows an adult person to instruct his or her doctor to withold or withdraw life-sustaining medical treatment if the person develops either a terminal illness or a permanent unconscious condition (such as an irreversible coma), if the life-sustaining treatment would only prolong the process of dying or the unconscious condition. However, treatment necessary to provide comfort and relieve pain would still be given.

This "living will" form is recommended for use by individuals who have not stated their treatment preferences in a Durable Power of Attorney for Health Care.

	Qty	Members	Non-members	Totals
California Natural Death Act Guidelines and Declaration	1	$2	$2	$ _____
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California Medical Association–PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-7, 1995, Disneyland Hotel, Anaheim.

Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. September 7-10, 1995, The Ritz Carlton Hotel, Aspen.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 5-8, 1995, Hyatt Regency Maui, Hawaii.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 19-21, 1995, Coeur d'Alene Resort.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 5-7, 1995, Village Red Lion, Missoula.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 27-30, 1995, Resort at Squaw Creek, 1995.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. May 12-13, 1995, Albuquerque.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 27-30, 1995. University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 28-30, 1995. Spokane Sheraton Hotel, Spokane, Washington.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 8-10, 1995, Jackson Lake Lodge, Moran.

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PRAVACHOL®

Pravastatin Sodium Tablets

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see **WARNINGS**).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of child-bearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. **Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals).** Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST, and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see **CONTRAINDICATIONS**). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see **CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism**). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see **ADVERSE REACTIONS**). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper normal limit, was rare (< 0.1%) in pravastatin clinical trials. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with another HMG-CoA reductase inhibitor is increased with concurrent therapy with either erythromycin, cyclosporine, niacin, or fibrates. However, neither myopathy nor significant increases in CPK levels have been observed in three reports involving a total of 100 post-transplant patients (24 renal and 76 cardiac) treated for up to two years concurrently with pravastatin 10-40 mg and cyclosporine. Some of these patients also received other concomitant immunosuppressive therapies. In one single-dose study, pravastatin levels were found to be increased in cardiac transplant patients receiving cyclosporine. Further, in clinical trials involving small numbers of patients who were treated concurrently with pravastatin and niacin, there were no reports of myopathy. Also, myopathy was not reported in a trial of combination pravastatin (40 mg/day) and gemfibrozil (1200 mg/day), although 4 of 75 patients on the combination showed marked CPK elevations versus one of 73 patients receiving placebo. There was a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy (see **PRECAUTIONS: Drug Interactions**). **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see **ADVERSE REACTIONS**). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (t $1/2$) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See **WARNINGS: Skeletal Muscle.**

Antipyrine: Since concomitant administration of pravastatin had no effect on the clearance of antipyrine, interactions with other drugs metabolized via the same hepatic cytochrome isozymes are not expected.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See **DOSAGE AND ADMINISTRATION: Concomitant Therapy.**)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Cyclosporine: Some investigators have measured cyclosporine levels in patients on pravastatin, and to date, these results indicate no clinically meaningful elevations in cyclosporine levels. In one single-dose study, pravastatin levels were found to be increased in cardiac transplant patients receiving cyclosporine.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* (1 hour prior to PRAVACHOL (pravastatin sodium)), *cimetidine, nicotinic acid*, or *probucol*, no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, ACE inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p < 0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥ 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p < 0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p < 0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/− mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X.: See **CONTRAINDICATIONS.**

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter^2). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (Vater association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with dextroamphetamine sulfate during the first trimester of pregnancy. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see **CONTRAINDICATIONS**).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time.

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

* Statistically significantly different from placebo.

The following effects have been reported with drugs in this class; not all the effects listed below have necessarily been associated with pravastatin therapy:

Skeletal: myopathy, rhabdomyolysis, arthralgia.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see **WARNINGS**).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See **WARNINGS: Skeletal Muscle** and **PRECAUTIONS: Drug Interactions.**)

OVERDOSAGE

To date, there are two reported cases of overdosage with pravastatin, both of which were asymptomatic and not associated with clinical laboratory abnormalities. If an overdose occurs, it should be treated symptomatically and supportive measures should be instituted as required.

Consult package insert before prescribing PRAVACHOL (pravastatin sodium).

(Revised 1-94) (J4-422E)

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Effective lipid management that's easy to live with

- Significantly reduces LDL-C up to 34% and total C up to 25%*
- Well tolerated with an excellent safety profile
- Suitable to use with many other medications
- Easy once-a-day dosing, with or without food

* With doses of 10 mg to 40 mg daily.

PRAVACHOL® (pravastatin sodium) is indicated as an adjunct to diet for the reduction of elevated total and LDL-C in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

Active liver disease or unexplained transaminase elevations, pregnancy, and lactation are contraindications to the use of pravastatin sodium.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.

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